PYRIDINE AND BENZOTHIAZOLE DERIVATIVES IN CARBANIONIC REACTIONS

By

JOSE MIGUEL AURRECOECHEA FERNANDEZ

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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Jose Miguel Aurrecoechea Fernandez

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Chairman: Alan R. Katritzky
Major Department: Chemistry

Carbanionic species derived from pyridinium salts, 2-alkoxypyridines and S-substituted benzothiazoles have been studied as intermediates in synthetic transformations.

Thus, ylides derived from 1-methyl- and 1-allyl-2,4,6-triphenylpyridinium salts formed aldol and Michael adducts; the aldol adducts were transformed into crotonaldehydes, α, β-unsaturated ketones and quinolizinium salts. The ylide derived from the corresponding 1-benzyl pyridinium salt rearranged to an azepine structure. Simple pyridinium salts transferred their N-substituent to hindered malonate anions and nitroamines.

2-Methylthiobenzothiazole and dithioacetals derived from 2-mercaptobenzothiazole were deprotonated at the active methyl and methylene positions, respectively, and the corresponding

carbanions reacted with electrophiles. 2-Methylthiobenzothiazole was used as a reagent for the mercaptomethylation of alkyl halides.

The benzothiazol-2-ylsulphenyl group was used as an ortho-directing substituent for the lithiation of the corresponding 2-substituted pyridine.

CHAPTER I
GENERAL INTRODUCTION

1.1 Carbanions

Carbanions are synthetically useful intermediates [79MI1]. Of particular theoretical and practical interest are those cases where certain groups appropriately disposed play an important role in the formation and/or stabilization of such species.

Thus, carbanions where the negative charge is dispersed by π conjugation to other atoms, inductive effect of α-heteroatoms or d orbital overlap have been widely used in synthesis. Coordination effects have also been important in the use of carbanions [83T1975].

All these considerations apply to heterocyclic systems, when suitably positioned to stabilize a carbanion. Here, however, the further manipulation of the heterocyclic moiety broadens the synthetic scope of the carbanionic reaction [84MI1].

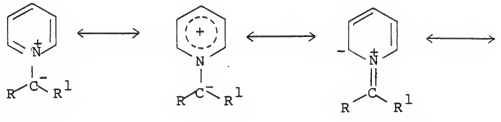
Some of the most common ways in which a heterocycle can facilitate carbanionic reactions include ylide formation, dipole stabilization and coordination effects. The general aspects of these different stabilizing effects are briefly discussed now.

1.1.1 Pyridinium Ylides

Among the ylides derived from heterocyclic compounds, pyridinium ylides (1.1) have found extensive application [76MI155].

The stability of these carbanionic species is due to the interaction between the carbanion and the adjacent positively charged heterocycle. This interaction is partially electrostatic, as represented by the resonance structure (1.2) where the electron pair of the sp^3 hybridized carbanionic center occupies one of the corners of a tetrahedron.

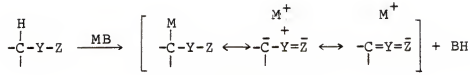
The alternative structure (1.3), where the carbanionic center is sp^2 hybridized and its two-electron p orbital interacts with the π electrons of the heteroaromatic system, also is an important contributor to the stabilization of the ylide.



(1.1) (1.2) (1.3)

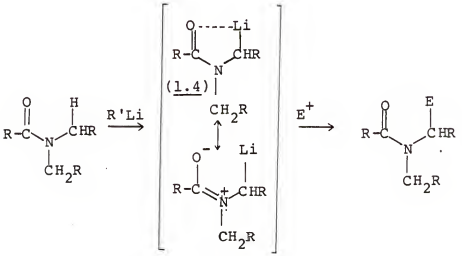
1.1.2 Dipole Stabilization

The field of dipole stabilized carbanions has been recently reviewed [78CR275, 84CR471]. In general terms, a carbanion is considered to be dipole stabilized when it is adjacent to a heteroatom which is the positive end of a dipole (Scheme 1.1).



Scheme 1.1

The possibility of dipole stabilization, however, does not necessarily mean that this contributes significantly to the stability of a given case [78CR275]. The carbanion could be simply stabilized by the inductive effect of the adjacent heteroatom and an additional chelating effect, as shown by (1.4) (Scheme 1.2).



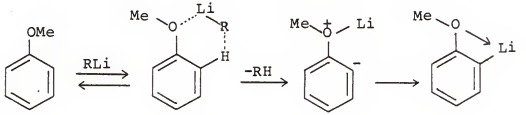
Scheme 1.2

1.1.3 Coordination Effects

Aromatic lithiation at the ortho position with respect to an electron donor group has been used as an alternative to the acid-catalized aromatic electrophilic substitution

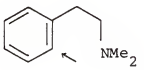
reactions that occur more at the para than at the ortho positions [83T1975, 83T2009]. Groups that have been used to direct lithiations include OMe, NMe_2, $NHCOBu^t$, $CONEt_2$ and oxazolines.

The mechanism of the ortho lithiation is shown in Scheme 1.3 [83T1975]. In the first step, the organolithium reagent complexes with the heteroatom present in the directing group. The ortho proton is then removed by the complexed reagent and, finally, Li enters the ortho position.



Scheme 1.3

It is interesting that the lithiation is also directed by groups in which the electron donor atom is one or two atoms away from the aromatic ring, as in (1.5).



(1.5)

1.2 General Overlook

In the following chapters the use of pyridinium salts, 2-alkoxypyridines and S-2-benzothiazole derivatives as precursors to carbanions stabilized by the effects mentioned above will be discussed.

A common and important feature in all the systems investigated here is that the heterocyclic moiety will be susceptible to removal after the carbanionic reaction has been performed. In the particular case of pyridinium salts this line received special attention and constitutes Chapter II of this dissertation.

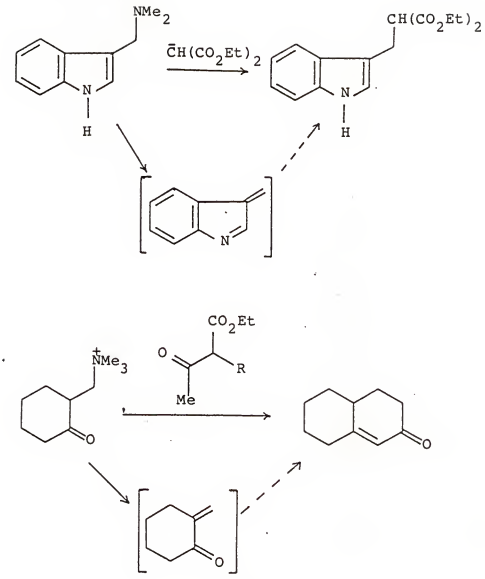
CHAPTER II
REACTIONS OF PYRIDINIUM SALTS WITH CARBON NUCLEOPHILES AND NITROAMINES

2.1 Introduction

2.1.1 Amines as Leaving Groups

Few general methods are reported in the literature for the nucleophilic displacement on amino groups as a means of converting them into other functionalities. Those possessing some general applicability are now summarized.

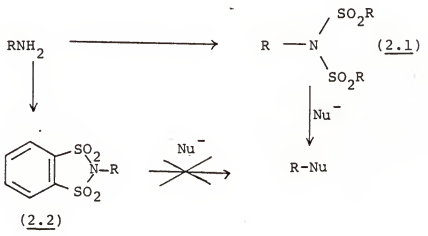
The alkylation of carbon nucleophiles by amines prepared by the Mannich reaction has been reviewed [53OR99]. Thus, amines of this type prepared from indole reacted with malonic ester derivatives resulting in the formal displacement of a secondary amine [45JA38] (Scheme 2.1). Displacement of a tertiary amine in quaternary ammonium salts of other Mannich bases has been used in a variation of the Robinson annulation with substituted acetoacetic esters [54JA4127] (Scheme 2.1). These reactions are thought to proceed via an elimination-addition mechanism [53OR99] (Scheme 2.1).



Scheme 2.1

Tertiary amines have been displaced from quaternary ammonium salts via an S_N2-type mechanism in compounds like benzyltrimethylammonium bromide where simple ß-elimination was not possible [530R99].

Some attempts have been made to convert primary amines into simple derivatives that could act as good leaving groups. Thus, n-hexylamine has been converted into the corresponding acetate via acyclic disulfonimides (2.1) (Scheme 2.2); however, the method failed when applied to cyclohexylamine [73SC297]. Earlier attempts with the cyclic disulfonimide derivatives (2.2) showed that these compounds are inert towards nucleophilic attack [69JO3434].



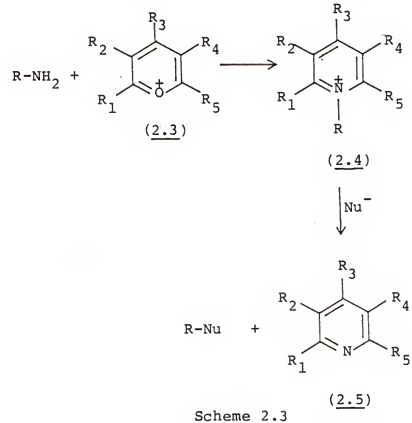
Scheme 2.2

2.1.2 Nucleophilic Displacements on Pyridinium* Salts

The work of Katritzky et al. over the last ten years [for reviews see 80T679, 84AG(E)420] has shown that primary amines can be converted into a large variety of different functionalities in a two-step sequence. This involves the

*Unless otherwise specified, the term "pyridinium" will include, throughout this work, pyridinium, quinolinium and acridinium salts. Likewise, "pyrylium" will be used as a general term for pyrylium and chromenylium salts.

initial reaction of the amine with a pyrylium salt (2.3) to form the corresponding pyridinium salt (2.4). In a second step this undergoes nucleophilic displacement of the pyridine leaving group (2.5) with transfer of the N-substituent to the incoming nucleophile (Scheme 2.3).

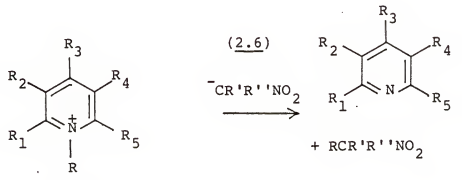


Scheme 2.3

2.1.3 Pyridinium Salts and Carbon Nucleophiles

The formation of carbon-carbon bonds upon reactions of pyridinium salts with carbon nucleophiles has been shown to hold significant promise. In particular, the transfer of the N-substituent from pyridinium salts (2.4) to nitronate anions (2.6) (Scheme 2.4) has been extensively studied both preparatively and mechanistically [81T25, 83JA90, 84T1501].

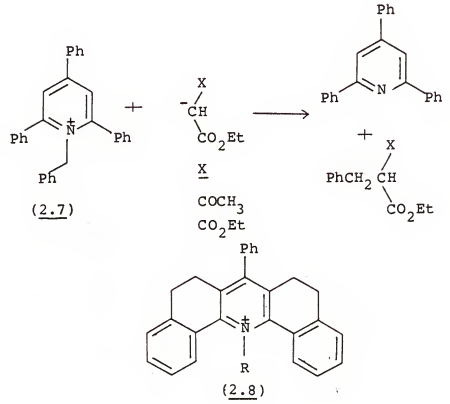
It provides a useful method for the carbon-alkylation of nitronate anions; a corresponding transformation is not possible with conventional alkylating agents, such as alkyl halides, because of the exclusive O-alkylation [79Cl].



Scheme 2.4

The analogous reactions with other types of carbanions have received comparatively little attention. Sodio-derivatives of diethyl malonate and ethyl cyanoacetate were benzylated by 1-benzyl-2,4,6-triphenylpyridinium salts (2.7) (Scheme 2.5), and, similarly, the transfer of N-alkyl substituents was possible with the more reactive [81JO3823] 1-alkyl-5,6,8,9-tetrahydro-7-phenyl-bis-benzo[a,h]acridinium salts (2.8) [80J(PI)661] . However, only one case has been reported where a more hindered nucleophile, diethyl ethylmalonate carbanion, has been benzylated with pyridinium salts [80TL1723]. There is no report on reactions involving

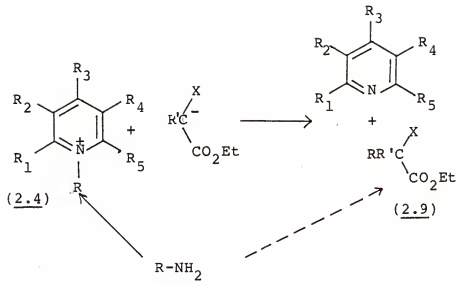
1-primary- or 1-secondary-alkyl pyridinium salts with hindered nucleophiles of the malonate type.



Scheme 2.5

2.1.4 Aim of the Work

It was intended to further study the reactivity of pyridinium salts with carbon nucleophiles and extend the applicability of this reaction by using hindered carbon nucleophiles. The proposed general reactions are shown in Scheme 2.6.



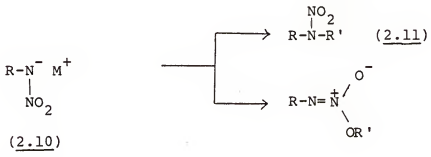
R	X
CH_2Ph	CO_2Et
n-alkyl	CN
sec-alkyl	$COCH_3$

Scheme 2.6

The reactions of 1-benzyl- and 1-primary-alkyl pyridinium salts with nucleophiles other than diethyl ethylmalonate carbanion would serve to generalize the previously reported analogous reaction [80TL1723] . Still more interesting was the possibility of reaction of diethyl ethylmalonate (and more hindered carbanions) with secondary-alkyl pyridinium salts. The corresponding reactions using alkyl halides as alkylating agents have been shown to proceed very sluggishly and to lead to considerable amounts of β-elimination products [51MI96, 42JA576, 42JA581]. Secondary-alkyl pyridinium salts give moderate yields of C-alkylation

products when reacted with nitronate anions [84T1501]. Therefore, the use of pyridinium salts as alkylating agents could be a useful method for the introduction of bulky groups on monoalkylmalonate anions. The overall conversion (2.4)-(2.9) (Scheme 2.6) would formally represent the displacement of a primary amino group by the carbanion.

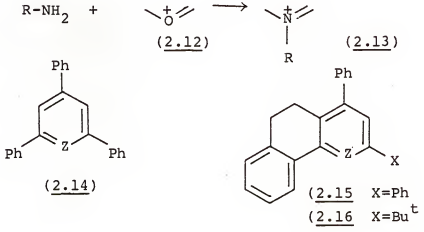
It was of interest to investigate whether the unusual selectivity shown by nitronate anions on the site of alkylation (C- vs. O-alkylation) [81T25] would be general for other ambident nucleophiles. The salts of primary nitroamines (2.10) appeared to be good substrates for this study (Scheme 2.7). Secondary nitroamines (2.11) cannot be conveniently prepared from these salts because of the competing O-alkylation that inevitably also takes place [69RCR640] (Scheme 2.7). It was hoped that pyridinium salts would afford good yields of the N-alkylated products (2.11).



Scheme 2.7

2.2 Results and Discussion

The pyridinium and quinolinium salts (2.13) were prepared from the corresponding pyrylium or chromenylium salts (2.12) and primary amines (Scheme 2.8), according to methods described in the literature [83J(PI)117, 80T679]. With the exception of (2.14h), all the pyrylium and pyridinium salts were known compounds and were identified by direct comparison of their melting points and spectral data with those of the specimens previously characterized in our research group (see experimental section).



	Z		Z
a	O^+	f	$\overset{+}{N}(i\text{-}C_3H_7)$
b	$\overset{+}{N}CH_2Ph$	g	$\overset{+}{N}(s\text{-}C_4H_9)$
c	$\overset{+}{N}(n\text{-}C_4H_9)$	h	$\overset{+}{N}(2\text{-}C_5H_{11})$
d	$\overset{+}{N}(n\text{-}C_7H_{15})$	i	$\overset{+}{N}(c\text{-}C_7H_{13})$
e	$\overset{+}{N}(n\text{-}C_8H_{17})$		

n=normal; i=iso; s=sec; c=cyclo

Scheme 2.8

Table 2.1 Pyrylium and pyridinium tetrafluoroborates

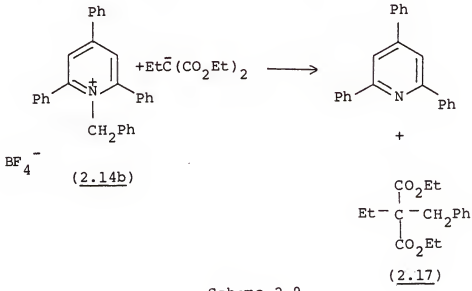
Compound	Yield(%)	M.p.(°C)	Lit. m.p.(°C)	Reference
(2.14a)	45	225-232	232-234	58BSF1458
(2.14b)	78	193-195	196-197	79J(PI)430
(2.14c)	75	195-197	201-202	79J(PI)430
(2.14e)	70	147-148	153-155	83MI85
(2.14h)	58	124-126[a]	-	-
(2.15a)	50	270-275	270	80J(PI)1895
(2.15f)	55	138-143	145-147	83J(PII)1443
(2.15g)	63	136-138	130-132	83J(PII)1443
(2.15h)	60	144-147	140-142	83J(PII)1443
(2.15i)	48	188-198[b]	211-214	83J(PII)1435
(2.16a)	65	189-193	179-185	79TH168
(2.16c)	70	143-145	142-144	79J(PI)430
(2.16d)	50	91-93	93-94	84T1501

a Found: C, 72.20; H, 6.06; N, 3.00. $C_{28}H_{28}BF_4N$ requires C, 72.28; H, 6.02; N, 3.01%.
b Found: C, 74.22; H,6.24; N, 2.69. $C_{32}H_{32}BF_4N$ requires C, 74.27; H, 6.18; N, 2.70%.

1-(2-Pentyl)-2,4,6-triphenylpyridinium tetrafluoroborate (2.14h) was characterized by its elemental (C, H, N) analysis and spectral (^{1}H-n.m.r., i.r.)properties. Thus, the infrared spectrum of (2.14h) showed strong bands at 1615 and 1050(b) cm^{-1}, corresponding to the C=N stretching frequency of the pyridinium ring and tetrafluoroborate anion, respectively. The α-hydrogen on the N-substituent appeared as a multiplet between 5.2 and 4.5 p.p.m. in the ^{1}H-n.m.r. spectrum. Physical and literature data for all pyrylium and pyridinium salts are given in Table 2.1.

2.2.1 Reactions with Carbon Nucleophiles

The reaction of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14b) with diethyl ethylmalonate anion had been previously reported to afford an 84% yield of the C-alkylated product (Scheme 2.9) [80TL1723].



(2.14b) (2.17)

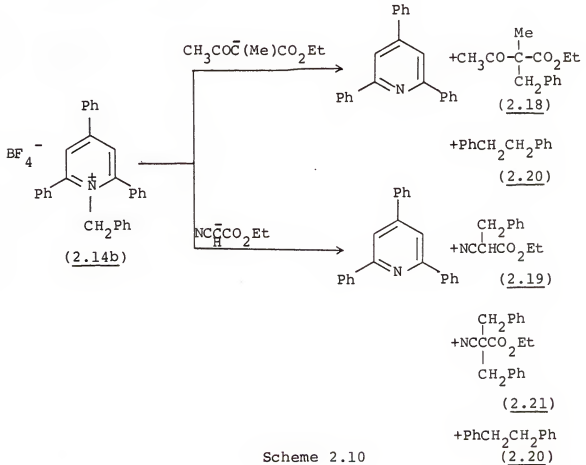
Scheme 2.9

A study of this reaction was undertaken to provide a model for future reactions. The expected product (2.17) was obtained in 50% yield when the reaction was carried out in refluxing toluene for 6h and 3 equivalents of the nucleophile were used. With equimolar amounts of the pyridinium salt and the nucleophile, the reaction failed to go to completion, even after prolonged heating for 13h, and the product was isolated in only 27% yield. Excess of the nucleophile (ca. 3 equivalents) was, therefore, used in all the reactions that were carried out subsequently.

Generally, the reaction conditions consisted of refluxing a mixture of the pyridinium salt and the preformed nucleophile in toluene for 1 to 7h, although heating at 50-90 ^{o}C in DMSO for 18 to 45h was preferred in some cases (Table 2.2). The progress of the reactions was monitored conveniently by t.l.c. (silica gel, chloroform). The pyridine (2.14; Z=N) or quinolines (2.15, 2.16; Z=N)(Scheme 2.8) that formed during the reaction were precipitated as the 1H-pyridinium or 1H-quinolinium chlorides and removed by filtration. The excess of starting ester was removed either by fractional distillation or by chromatography; when a highly branched product was made, the separation was achieved by selective hydrolysis of the monosubstituted ester [57QR157]. The products were further purified by distillation. Full details are given in the experimental section.

Reactions with 1-benzylpyridinium salts

The carbanions derived from ethyl 2-methylacetoacetate and ethyl 2-cyanoacetate reacted with 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14b) in DMSO at 50-60 °C to form the expected products (2.18) and (2.19) (Scheme 2.10) in 33 and 29% yield, respectively. In addition, small amounts of bibenzyl (2.20) were produced in both reactions. With ethyl 2-cyanoacetate, where two acidic protons are present, dialkylation also took place and (2.21) was obtained in 34% yield; in the latter reaction, DMSO and toluene could be used as solvents with the same result. As is described later (section 2.2.3), the reaction with ethyl 2-methylacetoacetate took an unexpected course when carried out in refluxing toluene.

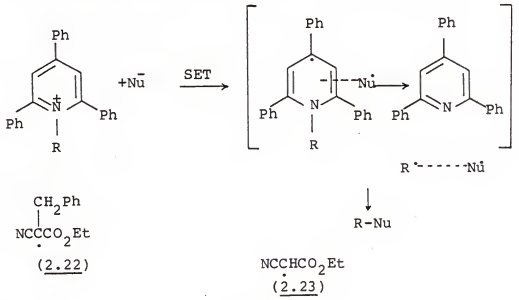


Scheme 2.10

Compounds (2.19) and (2.21) were known and their characterization was based on spectral (i.r. and ^{1}H-n.m.r.) properties (Table 2.3) and comparison of their boiling points with the values reported in the literature (Table 2.2). Bibenzyl was identified by comparison of its ^{1}H-n.m.r. spectrum with the reported spectrum [76MI1184].

The ester (2.18) showed a strong carbonyl absorption at 1740 cm^{-1} in the infrared spectrum. In its ^{1}H-n.m.r. spectrum the benzylic protons appeared as an AB quartet (J = 13 Hz) centered at 3.2 p.p.m. Its elemental analysis was consistent with the structure.

The formation of bibenzyl has some mechanistic relevance since it seems to imply the intervention of radicals in the reaction. Pyridinium salts are believed to react with nitronate anions via a non-chain radicaloid mechanism that is initiated by a single electron transfer (SET) from the carbanion to the pyridinium salt (Scheme 2.11) [83JA90].



Scheme 2.11

Table 2.2 Preparation of malonates, acetoacetates and cyanoacetates $R^1 R^2 C(R^3)CO_2Et$

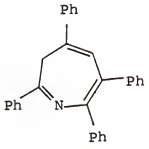
Pyridinium salt	R^1	R^2	R^3	Reaction time(h)	Yield (%)	B.p.(°C/mmHg)	Lit.b.p.(°C/mmHg)	Lit.yield (%)	Reference
(2.14b)	$PhCH_2$	Et	CO_2Et	7[a]	50	104-106/0.2	184/18	85	62BCJ1380
(2.14b)	$PhCH_2$	Me	$COCH_3$	18[b]	33	80/0.8[c]	-	-	-
(2.14b)	$PhCH_2$	H	CN	28[b]	29	102-104/0.8	160-165/11	44	69LA1
(2.14b)	$PHCH_2$	$PhCH_2$	CN	28[b]	34	140/0.8	190-200/15	6	44J13
(2.14c)	Et	Et	CO_2Et	-	-	54-56/0.6	88-90/5	-	76MI1879
(2.15f)	i-C_3H_7	Et	CO_2Et	1 1/4[a]	56	54-56/0.35	129.5-132.0/20	65	49JA835
(2.15f)	i-C_3H_7	s-C_4H_9	CO_2Et	42	37	76-80/0.5	120-123/10	26	42JA581
(2.15h)	2-C_5H_{11}	Et	CO_2Et	1 3/4[a]	40	70/0.3	123-124/10	71	69JHC203
(2.14h)	2-C_5H_{11}	Et	CO_2Et	2 1/2[a]	43	76/0.4	123-124/10	71	69JHC203
(2.15i)	c-C_7H_{13}	Et	CO_2Et	2 1/2[a]	20	100-104/0.55[d]	-	-	-

[a]Solvent: toluene; [b]Solvent: DMSO; [c]Found: C,71.54; H, 7.72. $C_{14}H_{18}O_3$ requires C,71.79; H, 7.69% [d]Found: M^+, 256.1686. Calculated for $C_{16}H_{28}O_4$: M^+, 256.1674

Pyridinium salts are known to be good electron acceptors [76MI4]; furthermore, a single electron transfer from the carbanions used here should be easier than from nitronate anions because of the lower oxidation potential of the former [64JA1807]. Therefore, the possibility of the SET mechanism is quite likely, and it would explain the formation of bibenzyl by a parallel mechanism to the one depicted in Scheme 2.11. This would also explain the significantly high incidence of dialkylation in the reaction with ethyl 2-cyanoacetate, when compared with the reaction using the alkyl halide as alkylating agent (Table 2.2), since the radical (2.22) derived from the monosubstituted product is more stable than the unsubstituted one (2.23) and would, therefore, form more readily (Scheme 2.11).

The formation of the above mentioned dialkylation product (2.21) contrasts with a previous report [80J(PI)661] where the same reaction, when carried out in 1,2-dimethoxyethane, gave the monoalkylated product in 68% yield exclusively.

As mentioned earlier, the reaction with ethyl 2-methylacetoacetate also showed a clear dependence on the conditions employed. In DMSO at 50 ^{o}C the desired product could be obtained; however, when the reaction was carried out in refluxing toluene the unexpected product (2.24) was isolated in 30% yield. The structure (2.24) is proposed on the bases of its elemental (C, H, N) analysis and spectral (i.r., u.v., ^{1}H-n.m.r., ^{13}C-n.m.r.) properties.



(2.24)

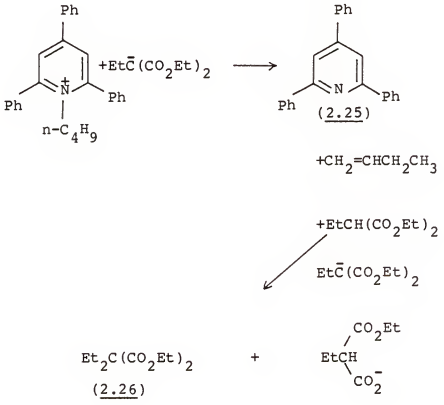
The structural elucidation of (2.24) and the mechanism for its formation will be dealt with in section 2.2.3.

Reaction with 1-primary-alkyl pyridinium salts

1-Primary-alkyl pyridinium salts failed to give any C-alkylation when reacted with the anions derived from diethyl ethylmalonate or diethyl methylmalonate. 2,4,6-Triphenylpyridine (2.25) was formed when pyridinium salts (2.14c) or (2.14e) were used; the absence of C-alkylation implied that the highly basic malonate anions promoted β-elimination as the main reaction pathway.

When forcing conditions were used, namely refluxing in xylenes for a prolonged time, the only product, other than 2,4,6-triphenylpyridine (2.25) (Scheme 2.12), that could be isolated was diethyl diethylmalonate (2.26). This product was identified by its spectral (i.r., ^{1}H-n.m.r.) properties (Table 2.3) and by comparison of its boiling point with the literature value (Table 2.2). Even the quinolinium salts (2.16; Z=$\overset{+}{N}$R), which had been found to be more reactive than any other pyridinium system in reactions with nitronate

anions [84Tl505], failed to give C-alkylation. Furthermore, when (2.16c) was refluxed in xylenes with diethyl ethylmalonate anion, the only C-alkylation product isolated was again diethyl diethylmalonate (2.26) together with the corresponding quinoline (2.16; Z=N).



Scheme 2.12

The formation of diethyl diethylmalonate is an example of the well-known dealkylation of esters by nucleophiles [76OR187] to form the corresponding acids (Scheme 2.13). In this particular case, the nucleophile diethyl ethylmalonate anion attacked the parent diethyl ethylmalonate

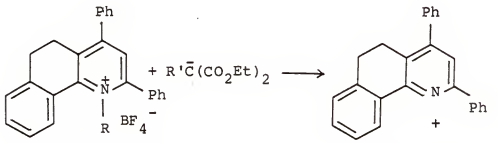
which was produced in the β-elimination reactions of the pyridinium salts (Scheme 2.12).

$$RCO_2\text{-}R' \quad + \quad Nu^- \quad \rightarrow \quad RCO_2^- \quad + \quad R'\text{-}Nu$$

Scheme 2.13

Reactions with 1-secondary-alkyl pyridinium salts

1-Alkyl-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium salts (2.15)(Scheme 2.14) were chosen for the transfer of secondary-alkyl groups since they react well in similar reactions with nitronate anions [84T1501].



(2.15)

	R	R'
a	i-C_3H_7	Et
b	i-C_3H_7	s-C_4H_9
c	2-C_5H_{11}	Et
d	c-C_7H_{13}	Et

$RR'C(CO_2Et)_2$

(2.27)

Scheme 2.14

Several secondary-alkyl quinolinium salts (2.15) (Scheme 2.14) on refluxing in toluene with the carbanions derived from diethyl ethylmalonate or diethyl s-butylmalonate gave the desired corresponding disubstituted malonic esters (2.27),

which were isolated in low to moderate yields (Scheme 2.14) (Table 2.2). Physical and spectral properties for the products are given in Tables 2.2 and 2.3, respectively.

The ester (2.27c) was also prepared in 43% yield from the corresponding 1-(2'-pentyl)-2,4,6-triphenylpyridinium salt (2.14h), suggesting that the nature of the pyridine leaving group does not materially affect the outcome of the reaction.

The yields (Table 2.2) decrease with both increasing substitution on the carbon directly attached to nitrogen and with the bulkiness of the nucleophile. This indicates that high basicity of the nucleophile and a hindered N-alkyl group facilitate elimination as an increasingly important side reaction [42JA581, 51MI96 and 68JO3477].

The reaction also proceeds at room temperature, as shown by the 37% yield obtained in the formation of (2.27b) (Table 2.2). However, the reaction seems to be severely limited in scope by the steric hindrance in the group to be transferred. Thus, under the same reaction conditions, only a 10% yield (estimated by ^{1}H-n.m.r.) of a rather impure product could be obtained when the corresponding 1-s-butylpyridinium salt (2.15g) was reacted with diethyl s-butylmalonate anion. The reaction could, nevertheless, offer the possibility of very mild overall conditions for the transfer of sensitive hindered groups from amines to relatively hindered carbon nucleophiles.

Table 2.3 I.r. and ^{1}H-n.m.r. spectra of malonates, acetoacetates and cyanoacetates $R^1R^2C(R^3)CO_2Et$

R^1	R^2	R^3	$\nu_{C=O}/\nu_{CN}$ (cm^{-1})	$CO_2CH_2CH_3$(q) δ	$CO_2CH_2CH_3$(t) δ	R^1 δ		R^2 δ		R^3 δ	
$PhCH_2$	Et	CO_2Et	1740(st) 1720(st)	4.2	1.2	$PhCH_2$ Ar	3.3(s) 7.2(s)	CH_3CH_2 CH_3CH_2	1.85(q) 0.9(t)	$CO_2CH_2CH_3$ $CO_2CH_2CH_3$	4.2(q) 1.2(t)
$PhCH_2$	CH_3	$COCH_3$	1740(st) 1710(st)	4.2	1.2	$PhCH_2$ Ar	3.2(ABq) 7.2(s)	1.3(s)		2.15(s)	
$PhCH_2$	H	CN	2260(w) 1750(st)	4.15	1.2	$PhCH_2$ Ar	3.5-3.7(m) 7.2(s)	3.3-3.05(m)			
$PhCH_2$	$PhCH_2$	CN	2260(w) 1745(st)	3.95	0.9	$PhCH_2$ Ar	3.15(ABq) 7.2(s)	$PhCH_2$ Ar	3.15(ABq) 7.2(s)		
Et	Et	CO_2Et	1730(st)	4.1	1.25	CH_3CH_2 CH_3CH_2	1.9(q) 0.8(t)	CH_3CH_2 CH_3CH_2	1.9(q) 0.8(t)	$CO_2CH_2CH_3$ $CO_2CH_2CH_3$	4.2(q) 1.2(t)
$i\text{-}C_3H_7$	Et	CO_2Et	1740(st) 1730(st)	4.05	1.15	$(CH_3)_2CH$ $(CH_3)_2CH$	2.2(m) 0.8(d)	CH_3CH_2 CH_3CH_2	1.85(q) 0.75(t)	$CO_2CH_2CH_3$ $CO_2CH_2CH_3$	4.05(q) 1.15(t)
$i\text{-}C_3H_7$	s-But	CO_2Et	1720(st)	4.15	1.25	$(CH_3)_2CH$ $(CH_3)_2CH$	2.55(m) 0.9(d)	2.4-0.8(m)		$CO_2CH_2CH_3$ $CO_2CH_2CH_3$	4.15(q) 1.25(t)
$2\text{-}C_5H_{11}$	Et	CO_2Et	1730(st)	4.1	1.25	2.4-0.7(m)		2.4-0.7(m)		$CO_2CH_2CH_3$ $CO_2CH_2CH_3$	4.1(q) 1.25(t)
$c\text{-}C_7H_{13}$	Et	CO_2Et	1725(st)	4.2	1.25	2.4-0.7(m)		2.4-0.7(m)		$CO_2CH_2CH_3$ $CO_2CH_2CH_3$	4.2(q) 1.25(t)

Note: I.r. spectra were recorded neat. ^{1}H-n.m.r. spectra were recorded in $CDCl_3$ solution; st=strong; w=weak; q=quartet; t=triplet; s=singlet; m=multiplet; d=doublet.

All products showed the expected spectral (i.r and ^{1}H-n.m.r.) properties (Table 2.3), and boiling points in agreement with the values reported in the literature (Table 2.2). One product, (2.27d), was previously unknown; it gave a satisfactory value for the accurate molecular weight in the high resolution mass spectrum (Table 2.2). The ^{13}C-n.m.r. data, when recorded, are given in the experimental section, and offer further support for the structures.

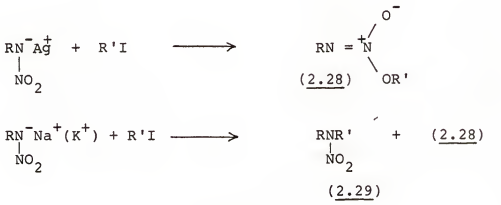
2.2.2 Reactions with Nitroamines

In recent years, interest in the chemistry of aliphatic nitroamines has risen, both because of interesting conversions of these compounds [51QR75] and because of a wide range of practical applications [65CA2662, 1897CB1248, 52CA6374, 59CA14533].

Aliphatic primary nitroamines can exist in two tautomeric forms (Scheme 2.15). Thorough physicochemical investigations [69RCR640] suggest that these compounds exist exclusively in the true nitroamine form in the un-ionized state.

Scheme 2.15

Primary aliphatic nitroamines are weak acids and form salts with bases [69RCR640]. The nitroamine anion is an ambident nucleophile with nucleophilic centers at both oxygen and nitrogen [69RCR640]. This anion can be alkylated with alkyl halides, the direction of the reaction depending significantly on the nature of the cation. Thus, the silver salts of nitroamines usually form O-alkylacinitroamines (2.28), whereas sodium or potassium salts form secondary nitroamines (2.29) (the N-alkylation products) preferentially, but always together with variable amounts of O-alkylation products (Scheme 2.16) [69RCR640].



Scheme 2.16

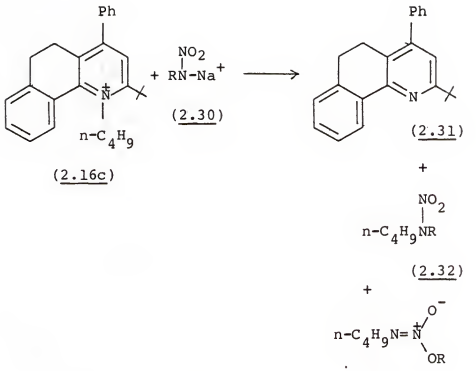
Therefore, the alkylation of salts of nitroamines with alkyl halides often cannot serve as a convenient method for obtaining secondary nitroamines. The problem is analogous to the one encountered in the alkylation of nitronate anions which give O-alkylation products with alkyl halides [79Cl].

Reactions were carried out between pyridinium salts and salts of nitroamines in the hope of obtaining exclusive N-alkylation. 1-Alkyl-2-t-butyl-5,6-dihydro-5-phenylbenzo[h]quinolinium salts (2.16; Z=$\overset{+}{N}$R)(Scheme 2.8) were again chosen for these reactions because of the high reactivity that they had shown with nitroanate anions [84T1501].

Methylnitroamine and butylnitroamine were prepared following literature procedures [49J1883, 55JA4387].

The reactions of the 1-n-butyl derivative (2.16c) with the sodium salts of methylnitroamine (2.30a) and of butylnitroamine (2.30b) (Scheme 2.17) were carried out in DMSO at 80-90 ^{o}C. 2-t-Butyl-5,6-dihydro-4-phenylbenzo[h]quinoline (2.31) was isolated together with the desired secondary nitroamines (2.32) in admixture with the corresponding isomeric O-alkyl-acinitroamines (2.33) (Scheme 2.17). The total yields obtained were 44% with methylnitroamine and 58% with butylnitroamine.

The mixtures were analyzed by ^{1}H-n.m.r. spectroscopy. The secondary nitroamines showed triplets for the α-methylene protons at 3.8 p.p.m.; the N-methyl group in (2.32a) resonated at 3.4 p.p.m. For the O-isomers, the O-C$\underline{H}_2$- protons appeared at 4.4 p.p.m. Distillation of the product mixture from the reaction with methylnitroamine afforded the secondary nitroamine in 20% yield. The boiling point of this was in agreement with the value reported in the literature [1895RTC1] and its infrared spectrum showed



	R
a	CH_3
b	$n\text{-}C_4H_9$

Scheme 2.17

strong bands at 1520 and 1290 cm^{-1} corresponding to the symmetrical and asymmetrical NO_2 stretching modes [69RCR640].

The product mixture from the reaction with the sodium salt of butylnitroamine was further analyzed by g.c.-mass spectroscopy. The molecular ions of both fractions confirmed

that it was indeed an isomeric mixture. Furthermore, the mass spectrum of one of the components of the mixture matched with the spectrum given in the literature [74MI657] for dibutylnitroamine (2.32b). More spectral data are given in the experimental section.

The integration of the ^{1}H-n.m.r. spectra of the O-C$\underline{H}_2$ vs. the (NO_2)N-C$\underline{H}_2$ protons gave the ratio of N- to O-isomers. This ratio was 3:1 for the (32a)-(33a) mixture and 7:10 for the (32b)-(33b) mixture. The amount of O-alkylation increases with the size of the alkyl substituent in the primary nitroamine. This could be expected since oxygen is a more accessible nucleophilic center than nitrogen in the nitroamine salt.

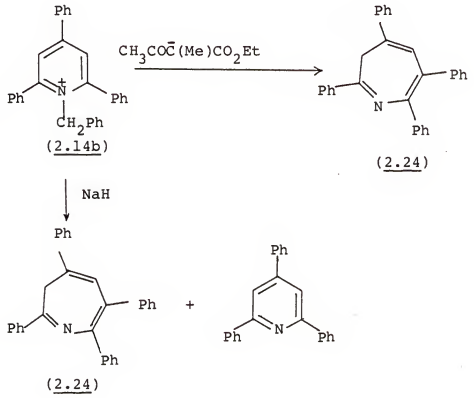
When the sodium salt of methylnitroamine was reacted with the pyridinium or quinolinium salts (2.14e) and (2.16d), the products corresponding to N- and O-alkylation were still formed but the main product of the reaction seemed to be a long chain hydrocarbon as deducted from ^{1}H-n.m.r. inspection of the crude reaction mixture; the separation of these mixtures was not attempted.

2.2.3 Formation of an Azepine

Structure elucidation

As mentioned in section 2.2.1, 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14b), on refluxing in toluene with the carbanion derived from ethyl 2-methylacetoacetate,

gave 3H-2,4,6,7-tetraphenylazepine (2.24) as a yellow crystalline solid (Scheme 2.18). The same compound was independently prepared in 30% yield by refluxing the pyridinium salt with excess sodium hydride in toluene; under these conditions, 2,4,6-triphenylpyridine was also obtained (Scheme 2.18).



Scheme 2.18

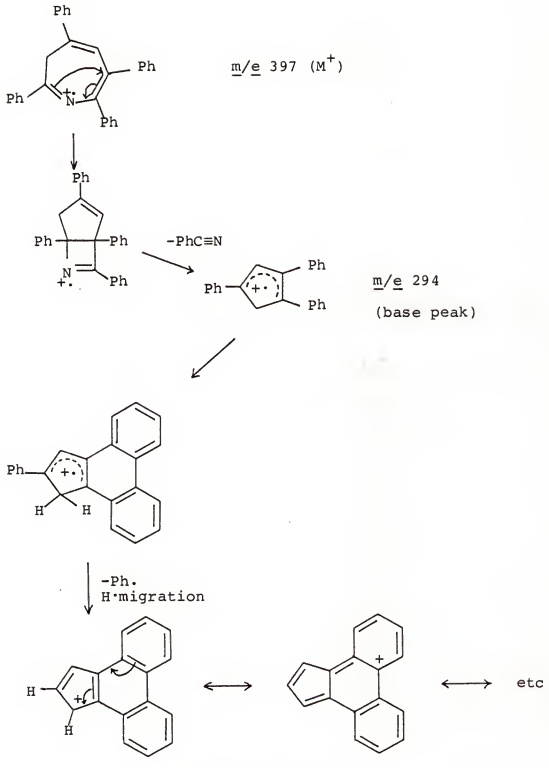
The infrared spectrum of (2.24) shows the absence of bands at 1620-1610 cm^{-1} (typical of pyridinium salts) and at 1050 cm^{-1} (due to the tetrafluoroborate anion).

In the ^{1}H-n.m.r. spectrum, aromatic absorptions are found between 8.0 and 7.2 p.p.m.; the olefinic proton resonates at 6.75 p.p.m. as a singlet and the geminal methylene protons appear as two doublets at 5.0 and 2.1 p.p.m. with a characteristic coupling constant of 11 Hz. The ^{13}C-n.m.r. spectrum is consistent with the structure and shows one aliphatic carbon that in the off-resonance spectrum resonates as a triplet.

The ultraviolet spectrum displays absorptions at 262 and 348 nm; the latter band extends into the visible region and is responsible for the light yellow color of this compound.

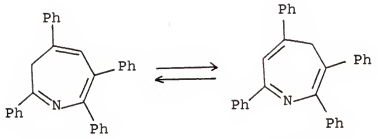
The mass spectrum (Scheme 2.19) shows a very intense molecular ion peak at m/e 397; loss of benzonitrile gives the base peak at m/e 294; loss of a phenyl group from the base peak, coupled with intramolecular cyclization to give a very stabilized ion (2.34), explains the other prominent fragment at m/e 215.

These data clearly point to an azepine structure, however they do not allow the distinction between the 3H-azepine (2.24) and the 4H-isomer (2.35) (Scheme 2.20). Structure (2.24) has been assigned on the basis of the greater stability of 3H-azepines [84MI492] and the fact that 4H-azepines rearrange easily to the corresponding 3H-tautomers under thermal or base-catalyzed conditions [72CB982].



(2.34) m/e 215

Scheme 2.19

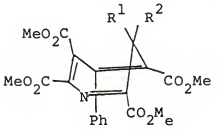


(2.24) (2.35)

Scheme 2.20

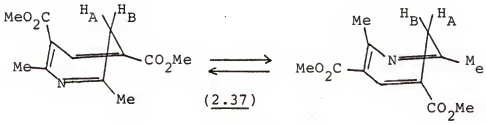
Conformational aspects

X-Ray crystallographic analyses on 3H-azepines [84MI494] have demonstrated that these compounds are non-planar and exist in a boat conformation where two of the double bonds are in the same plane as shown for the azepine (2.36).



(2.36)

The two stable boat forms which are possible are interconvertible by ring inversion of the azepine ring. The energy barrier for ring inversion has been measured in several cases and can be relatively high when the azepine ring is highly substituted. As an example, the $\Delta G^{\ddagger}$ for ring inversion in the 3H-azepine (2.37) is 13.6 kcal·mol^{-1} [71JO978] (Scheme 2.21).



Scheme 2.21

In our case, the ^{1}H-n.m.r. pattern of two doublets for the geminal methylene protons indicates that a single conformer is present at room temperature in chloroform solution. Increasing the temperature of the sample results in broadening of the signals, as a consequence of the ring inversion (Figure 2.1), and coalescence is observed at 80 °C. From this value, the $\Delta G^{\ddagger}$ for ring inversion is calculated [82MI96] to be 16.3 kcal·mol^{-1}.

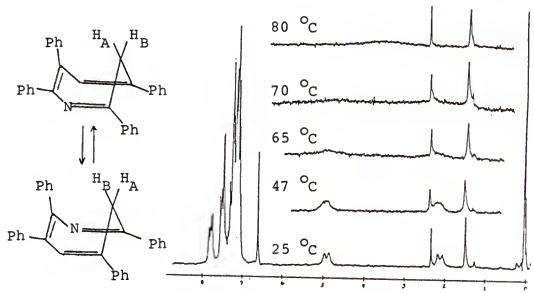
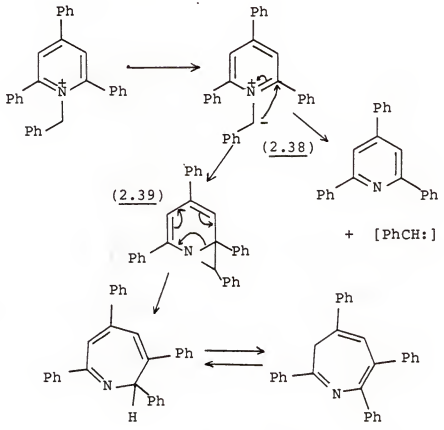


Figure 2.1 Variable temperature ^{1}H-n.m.r. spectra of 3H-2,4,6,7-tetraphenylazepine

Mechanism of formation

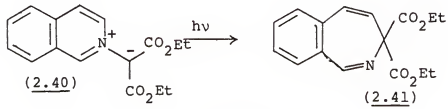
The proposed mechanism for the formation of the azepine (2.24) is depicted in Scheme 2.22. Under basic conditions, formation of the ylide (2.38) takes place. This ylide can decompose to form phenylcarbene and the other observed product, 2,4,6-triphenylpyridine. Carbene formation has been previously observed [76TL3081] in the photolysis of quinolinium ylides.



Scheme 2.22

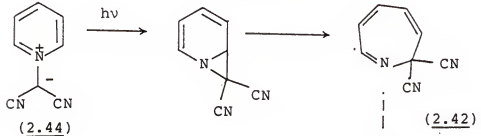
Alternatively, the ylide can attack the α-position of the pyridinium ring to form the bicyclic structure (2.39) which undergoes Cope rearrangement followed by tautomerization to afford the observed product.

A similar type of ring expansion has been reported in the photolysis of the quinolinium ylide (2.40) to give the benzazepine (2.41) (Scheme 2.23) [76TL3081]. Similarly, the azepine (2.42) was suggested as an intermediate in the formation of pyrrole (2.43) during the photolysis of the pyridinium ylide (2.44) (Scheme 2.24) [77PAC305].

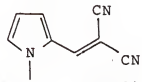


(2.40) (2.41)

Scheme 2.23

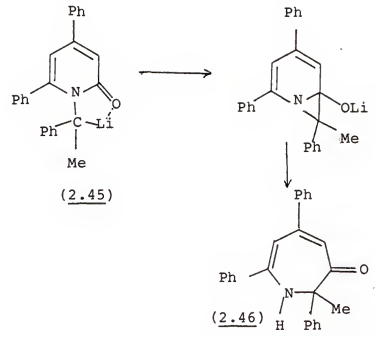


(2.44) (2.42)



Scheme 2.24 (2.43)

More recently, the 2-pyridone carbanion (2.45) was reported to rearrange to the azepinone (2.46) by attack on the carbonyl group followed by Cope rearrangement and protonation (Scheme 2.25) [80J(PI)2851]. However, there is apparently no report in the literature on the synthesis of monocyclic azepines from pyridinium ylides.



Scheme 2.25

2.3 Conclusions

Monosubstituted malonate, acetoacetate and cyanoacetate carbanions can be benzylated in moderate to low yields by pyridinium salts. The method, however, does not represent an advantage over existing methods in the literature since the yields are lower than those previously reported (Table 2.2).

The formation of bibenzyl in these reactions indicates that, at least to some extent, radicals are formed during the course of the reaction.

N-Secondary-alkyl pyridinium salts also transfer their N-substituents to hindered malonate anions in moderate to low yields. These yields are again generally lower than those obtained by conventional literature methods (Table 2.2). Although limited in scope, the reaction proceeds at room temperature. The formation of the pyridinium salts also takes place at room temperature [82J(PI)117]. Therefore, the overall sequence is potentially a method for the transfer of sensitive hindered groups from amines to relatively hindered carbon nucleophiles under mild conditions.

Salts of primary nitroamines react with pyridinium salts to give a mixture of the secondary nitroamine and the isomeric O-alkylacinitroamines, this behavior parallels that shown by alkyl halides in the same type of reaction.

Under the conditions employed for alkylation, 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate undergoes ring expansion to form an azepinoid compound that has been assigned the structure of 3H-2,4,6,7-tetraphenylazepine, although the corresponding 4H-tautomer cannot be completely excluded. A ring inversion barrier of 16.3 $kcal \cdot mol^{-1}$ has been calculated for this azepine. The intermediacy of a pyridinium ylide in the formation of the azepine is postulated. This is potentially a new method for the synthesis of azepines.

2.4 Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded

on a Perkin-Elmer 283B spectrophotometer; u.v. spectra were obtained on a Pye-Unicam PU 8800 spectrophotometer; 60 MHz ^{1}H-n.m.r. spectra were recorded on a Varian A-60A, a Varian EM 360L or a Jeol JNM-PMX60 spectrometer; the variable temperature 100 MHz ^{1}H-n.m.r. spectra and 25 MHz ^{13}C-n.m.r. spectra were recorded on a Jeol JNM-FX 100 spectrometer, and the g.c./mass spectroscopy results were obtained by Dr. R. W. King, on a AEI MS 30 spectrometer.

Dichloromethane was stored over calcium chloride or 4Å molecular sieves; dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over 4Å molecular sieves; toluene was stored over sodium wire or 5Å molecular sieves; xylenes were stored over sodium wire.

The following compounds were prepared according to literature methods: 2,4,6-triphenylpyrylium tetrafluoroborate (2.14a) (45%), m.p. 225-232 °C (lit. [58BSF1458] m.p. 232-234 °C); 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14b) (78%), m.p. 193-195 °C (lit. [79J(PI)430] m.p. 196-197 °C); 1-n-butyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14c) (75%), m.p. 195-197 °C (lit. [79J(PI)430] m.p. 201-202 °C); 1-n-octyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14e) (70%), m.p. 147-148 °C (lit. [83MI85] m.p. 153-155 °C); 2-t-butyl-5,6-dihydro-4-phenylbenzo[h]chromenylium tetrafluoroborate (2.16a) (65%), m.p. 189-193 °C (lit. [79TH168] m.p. 179-185 °C); 1-n-butyl-2-t-butyl-5,6-dihydro-4-phenylbenzo[h]-quinolinium tetrafluoroborate (2.16c) (70%), m.p. 143-145 °C

(lit.[79J(PI)430] m.p. 142-143 °C); 1-n-heptyl-2-t-butyl-5,6-dihydro-4-phenylbenzo[h]quinolinium tetrafluoroborate (2.16d) (50%), m.p. 91-93 °C (lit. [84T1501] m.p. 93-94°C); 5,6-dihydro-2,4-diphenylbenzo[h]chromenylium tetrafluoroborate (2.15a) (50%), m.p. 270-275 °C (lit. [80J(PI)1895] m.p. 270 °C); 1-isopropyl-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium tetrafluoroborate (2.15f) (55%), m.p. 138-143 °C (lit. [83J(PII)1443] m.p. 145-147 °C); 1-(2'-pentyl)-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium tetrafluoroborate (2.15h)(60%), m.p. 144-147 °C (lit. [83J(PII)1443] m.p. 140-142 °C); 1-cycloheptyl-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium tetrafluoroborate (2.15i) (48%), m.p. 188-198 °C (lit. [83J(PII)1435] m.p. 211-214 °C) (Found: C, 74.22; H, 6.24; N, 2.69. $C_{32}H_{32}BF_4N$ requires C, 74.27; H, 6.18; N, 2.70%); diethyl s-butylmalonate, b.p. 76-78 °C/2 mmHg (lit. [78MI530] b.p. 120 °C/20 mmHg); 1-s-butyl-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium tetrafluoroborate (2.15g)(63%), m.p. 136-138 °C (lit. [83J(PII)1443] m.p. 130-132 °C); methylnitroamine (61%), m.p. 29-31 °C(lit. [49JI883] m.p. 32-36 °C); butylnitroamine (90%), b.p. 96-98 °C/0.55 mmHg (lit. [55JA4387] b.p. 68-70 °C/0.05 mmHg).

2.4.1 Reactions with Carbon Nucleophiles

Reaction of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14b) with diethyl ethylmalonate anion

Diethyl ethylmalonate (5.64 g; 30 mmol) was added to a solution of sodium (0.69 g; 30 mmol) in absolute ethanol (12 ml) and the solvent was removed under reduced pressure (20 mmHg). The remaining white solid was dried under vacuum

(1 mmHg), mixed with 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (4.85 g; 10 mmol) and toluene (25 ml), and the mixture refluxed for 7h. After cooling, the reaction mixture was filtered, water added to the filtrate and the whole extracted with ether; the combined organic extracts were washed with water and dried ($MgSO_4$). Dry hydrochloric acid was passed through the solution and 1H-2,4,6-triphenylpyridinium chloride collected by filtration. The filtrate was evaporated under reduced pressure (20 mmHg) and the residual oil, which consisted of diethyl ethylmalonate and diethyl benzylethylmalonate, fractionally distilled to yield 1.4 g (50%) of diethyl benzylethylmalonate, b.p. 104-106 °C/0.2 mmHg (lit. [62BCJ1380] b.p. 184 °C/18 mmHg); the spectral data (i.r., ^{1}H-n.m.r.) are recorded in Table 2.3.

Reaction of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate(2.14b) with ethyl 2-methylacetoacetate anion

Ethyl 2-methylacetoacetate (2.5 g; 17 mmol) was added to a stirred suspension of sodium hydride (0.416 g; 17 mmol) in dimethyl sulfoxide (15 ml) upon which hydrogen was rapidly evolved. Once the evolution of hydrogen had ceased, 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.8 g; 5.78 mmol) was added and the resulting dark solution was stirred at 50 °C for 18h. After cooling, water (15 ml) was added, the solution filtered, extracted with water, and the organic extracts washed several times with water and dried ($MgSO_4$). Dry hydrochloric acid was bubbled through the solution to precipitate

1H-2,4,6-triphenylpyridinium chloride, which was filtered out. The filtrate was evaporated under reduced pressure (20 mmHg) and the remaining oil distilled. Ethyl 2-benzyl-2-methylacetoacetate distills at 90 ^{o}C/0.8 mmHg together with some bibenzyl ($PhCH_2CH_2Ph$) (lit. [29MIlll], b.p. 284.9 ^{o}C). These two products were separated by column chromatography on silica gel with methylene chloride as eluent. Ethyl 2-benzyl-2-methylacetoacetate (0.450 g; 33%) distilled then at 80 ^{o}C/0.8 mmHg (Found: C, 71.54; H, 7.72. $C_{14}H_{18}O_3$ requires C, 71.79; H, 7.69). The spectral data (i.r., ^{1}H-n.m.r.) are recorded in Table 2.3.

Reaction of 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14b) with ethyl 2-cyanoacetate anion

Ethyl 2-cyanoacetate (2.03 g; 18 mmol) was added to a solution of sodium hydride (0.43 g; 18 mmol) in absolute ethanol (10 ml) upon which a solid immediately formed; the solvent was completely removed under reduced pressure (20 mmHg), the solid dried under vacuum (1 mmHg), mixed with 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.91 g; 6 mmol) and the mixture dissolved in dimethyl sulfoxide (10 ml). The strongly brown solution that resulted was stirred at 50-60 ^{o}C for 28h. After cooling, water (10 ml) was added and the solution extracted with ether (3 x 20 ml); the organic extracts were washed with water (5 times) and dried ($MgSO_4$). Dry hydrochloric acid was bubbled through the solution and 1H-2,4,6-triphenylpyridinium chloride removed by filtration.

The filtrate was evaporated and the remaining crude oil chromatographed on silica gel using dichloromethane:hexanes (8:2) as eluent. In successive order of elution the following products were obtained: bibenzyl ($PhCH_2CH_2Ph$); 2,4,6-triphenylpyridine, m.p. 128-130 °C (lit. [82J(PII)1041] m.p. 135-136 °C); ethyl 2-benzyl-2-cyano-3-phenylpropionate (0.3 g; 34%), b.p. 140 °C/0.8 mmHg (lit. [44J13] b.p. 190-200 °C/15 mmHg) and ethyl 2-cyano-3-phenylpropionate (0.35 g; 29%), b.p. 102-104 °C/0.8 mmHg (lit. [69LA1] b.p. 160-165 °C/11 mmHg). the spectral data (i.r., ^{1}H-n.m.r.) for the products are recorded in Table 2.3.

Attempted preparation of diethyl n-butylethylmalonate

Diethyl ethylmalonate (2.47 g; 13.1 mmol) was added to a stirred suspension of NaH (0.31 g; 13.1 mmol) in xylenes (20 ml) and the mixture slightly warmed until evolution of hydrogen had ceased and a white precipitate had formed. 1-n-Butyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.14c) (2 g; 4.3 mmol) [or the equivalent amount of (2.14e) or (2.16c)] was then added and the mixture stirred and refluxed for 21h. After cooling, the mixture was filtered, the filtrate washed with water, the aqueous layer extracted with ether, and the organic extracts combined and dried ($MgSO_4$). The solvents were removed under pressure (20 mmHg) and the crude material chromatographed on silica gel; elution with xylenes afforded 2,4,6-triphenylpyridine; further elution with hexanes:methylene chloride (3:2) gave diethyl diethylmalonate

(0.5 g; 41%, based on starting diethyl ethylmalonate), b.p. 54-56 °C/0.6 mmHg (lit. [76MI1879] b.p. 88-90 °C/5 mmHg). Spectral data (i.r., ^{1}H-n.m.r.) are given in Table 2.3.

General method for the reaction of 1-secondary-alkyl-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium tetrafluoroborates (2.15; Z = $\overset{+}{N}$R) with diethyl ethylmalonate anion

Diethyl ethylmalonate (2.43 g; 12.9 mmol) was added to a suspension of sodium hydride (0.31 g; 12.9 mmol) in toluene (20 ml) and the mixture was gently warmed until evolution of hydrogen had ceased and a white solid had formed. The corresponding quinolinium salt (2.15f, 2.15h or 2.15i) (4.3 mmol) was added and the mixture refluxed and stirred for the appropriate time (Table 2.2). After cooling, the reaction mixture was filtered and the solvent removed under reduced pressure (20 mmHg). The crude material was dissolved in ether (50 ml) and dry hydrochloric acid was bubbled through the solution. 1H-5,6-Dihydro-2,4-diphenylbenzo[h]quinolinium chloride was removed by filtration. The solvent was evaporated and the remaining liquid chromatographed on silica gel to afford the disubstituted malonate esters that were distilled under reduced pressure: diethyl ethylisopropylmalonate (2.27a) (56%) was obtained from quinolinium salt (2.15f) by elution with benzene:hexanes (3:1), b.p. 54-56 °C/0.35 mmHg (lit. [49JA835] b.p. 129.5-132.0 °C/20 mmHg); diethyl ethyl(2-pentyl)malonate (2.27c) (40%), obtained from (2.15h), was eluted with hexanes:methylene chloride (3:1), b.p. 70 °C/0.3 mmHg (lit. [69JHC203] b.p. 123-124 °C/10 mmHg); diethyl

cycloheptylethylmalonate (2.27d)(20%) prepared from (2.15i), was eluted with hexanes:methylene chloride (3:1), b.p. 100-104 °C/0.55 mmHg (Found: M^+, 256.1686; calculated for $C_{16}H_{28}O_4$: M^+, 256.1674). Spectral data (i.r., ^{1}H-n.m.r.) are given in Table 2.3; δ_c (p.p.m.) ($CDCl_3$): (2.27c) 170.88(s), 170.71(s), 62.24(s), 60.25(t), 36.44(d), 35.10(t), 26.79(t), 21.35(t), 14.91(q), 14.15(q), 9.18(q); (2.27d) 171.06(s), 62.20(s), 60.19(t), 42.50(d), 29.78(t), 27.49(t), 26.81(t), 13.8(q), 9.07(q).

Preparation of 1-(2'-pentyl)-2,4,6-triphenylpyridinium tetrafluoroborate (2.14h)

2-Pentylamine (2.19 g; 25.2 mmol) was added with stirring to a suspension of 2,4,6-triphenylpyrylium tetrafluoroborate (5 g; 12.26 mmol) in dichloromethane (40 ml). The solution was stirred at room temperature for 40 min. Acetic acid (1.51 g; 25.2 mmol) was then added and the mixture stirred further 14h at room temperature. The solvent was partially removed under reduced pressure (20 mmHg) to a volume of ca. 10 ml. This solution was poured into diethyl ether (ca. 150 ml) to give an oil that upon stirring crystallized to afford 3.4 g (58%) of product. It was crystallized from ethanol-diethyl ether as white needles, m.p. 124-126 °C. (Found: C, 72.20; H, 6.06; N, 3.00%. $C_{28}H_{28}BF_4N$ requires C, 72.28; H, 6.02; H, 3.01%); ν_{max} (cm^{-1}) ($CHBr_3$) 1615(s), 1595(s), 1560(s), 1490(m), 1443(m), 1050(s,b); δ (p.p.m.) ($CDCl_3$) 8.1-7.1 (17H, m), 5.2-4.5 (1H, m), 2.1-0.9 (10H, m).

Reaction of 1-(2'-pentyl)-2,4,6-triphenylpyridinium tetrafluoroborate (2.14h) with diethyl ethylmalonate anion

The general method used with 1-secondary-alkyl quinolinium salts was applied here. Diethyl ethyl(2-pentyl)-malonate was obtained in 43% yield after chromatography in silica gel (hexanes:methylene chloride, 3:1), b.p. 76 °C/ 0.4 mmHg (lit. [69JHC203] b.p. 123-124 °C/10 mmHg).

Reaction of 1-isopropyl-5,6-dihydro-2,4-diphenylbenzo[h]-quinolinium tetrafluoroborate (2.15f) with diethyl s-butyl-malonate anion

Diethyl s-butylmalonate (6.48 g; 30 mmol) was added to a stirred suspension of sodium hydride (0.72 g; 30 mmol) in toluene (30 ml) and the mixture warmed to 60 °C until hydrogen was evolved and a white precipitate formed; after cooling to room temperature 1-isopropyl-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium tetrafluoroborate (4.62 g; 10 mmol) was added and the mixture stirred at room temperature for 42h, after which it was filtered, dry hydrochloric acid bubbled through the solution and the precipitated 1H-5,6-dihydro-2,4-diphenylbenzo[h]quinolinium chloride removed by filtration. The filtrate was evaporated and the residual oil was treated with 50% KOH (20 ml) at 80 °C for 2h. After cooling, the two layers were separated, the aqueous layer extracted with ether, and the combined organic layers washed with water and dried ($MgSO_4$). Evaporation of the solvent left an oil that was distilled to afford diethyl isopropyl-s-butyl-malonate (0.95 g; 37%), b.p. 76-80 °C/0.5 mmHg (lit. [42JA581]

b.p. 120-123 °C/10 mmHg). The spectral data (i.r., ^{1}H-n.m.r.) are given in Table 2.3; δ_C (p.p.m.) ($CDCl_3$) 169.94(s), 169.84 (s), 65.88(s), 59.94(t), 37.13(d), 29.77(d), 25.72(t), 18.66 (q), 17.73(q), 13.88(q), 13.79(q), 12.62(q).

2.4.2 Reactions with Nitroamines

General method for the reactions of 1-alkyl-2-t-butyl-5,6-dihydro-4-phenylbenzo[h]quinolinium tetrafluoroborates (2.16; Z = NR) with alkylnitroamine anions

The appropriate primary nitroamine (30 mmol) in absolute ethanol (15 ml) was added to a solution of sodium hydride (30 mmol) in absolute ethanol (15 ml), upon which the sodium salt of the nitroamine precipitated immediately; the solvent was removed under reduced pressure (20 mmHg) and the resulting solid dried under vacuum (1 mmHg). The quinolinium salt (10 mmol) was then mixed with it and the whole dissolved in dimethyl sulfoxide (20 ml) and stirred at 80-90 °C for 28-45h. After cooling, the reaction mixture was poured into water (20 ml), extracted with ether (3 x 15 ml), and the organic extracts thoroughly washed with water and dried ($MgSO_4$). Dry hydrochloric acid was bubbled through the solution, while cooling this in an ice bath. The precipitated 1H-2-t-butyl-5,6-dihydro-4-phenylbenzo[h]quinolinium chloride was removed by filtration and the filtrate evaporated to give the crude mixture of the secondary nitroamine and the isomeric O-alkylacinitroamines. The reaction between 1-n-butyl-2-t-butyl-5,6-dihydro-4-phenylbenzo[h]quinolinium tetrafluoroborate (2.16c) and methylnitroamine (reaction time: 28h) afforded, after

distillation of the crude product, N-methyl-N-nitrobutylamine (20%), b.p. 50-60 °C/0.15 mmHg (lit. [1895RTC1] b.p. 107 °C/15 mmHg); ν_{max} (cm^{-1}) (neat) 1520(s), 1290(s); δ (p.p.m.) ($CDCl_3$) 3.8 (2H, t, J = 6 Hz), 3.4 (3H, s), and 2.0-0.7 (7H, m); δ_c (p.p.m.) ($CDCl_3$-CCl_4) 52.1(t), 38.1(q), 28.0(t), 19.4 (t), and 13.2(q). From the reaction of (2.16c) with butylnitroamine (reaction time: 45h), distillation of the crude product afforded dibutylnitroamine and N-butyl-O-butylacinitroamine in 58% total yield, b.p. 58-60 °C/0.9 mm (lit. [48CJR114] b.p.'s 127-130 °C/11 mmHg and 97-98.7 °C/11 mmHg respectively); ν_{max} (cm^{-1}) (neat) 1550(s), 1510(s), 1280(s), 1240(s); δ (p.p.m.) ($CDCl_3$) 4.4 2H, t, J = 6 Hz, N-O-CH_2), 3.85 (4H, t, J = 6 Hz, -CH_2-N-NO_2), 3.5 (2H, t, J = 6 Hz, -CH_2-N=N), 2.1-0.8 (m); δ_c (p.p.m.) ($CDCl_3$) 69.8 (t, CH_2-O-N), 52.8 (t, CH_2-N-NO_2 or CH_2-N=N), 51.1 (t, CH_2-N=N or CH_2-N-NO_2), 28.9(t), 28.8(t), 28.3(t), 20.3(t), 19.6(t), 18.7(t), 13.2(q). G.c-mass spectroscopy: dibutylnitroamine m/e (%) 131(24.1), 86(22.8), 85(12.4), 84(100), 70(9.9), 57(33), 56(16.1), 43(67.2), 42(54.4), 41(45.3), 39(13.1) (identical to literature spectrum [74MI657].

2.4.3 Azepine Formation

Preparation of 3H-2,4,6,7-tetraphenylazepine (2.24)

1-Benzyl-2,4,6-triphenylpyridinium tetrafluoroborate (2.2 g; 4.58 mmol) was added to a stirred suspension of 97% sodium hydride (0.17 g; 6.87 mmol) in dry toluene (15 ml). The mixture was refluxed in an oil bath at 125-130 °C for 45h.

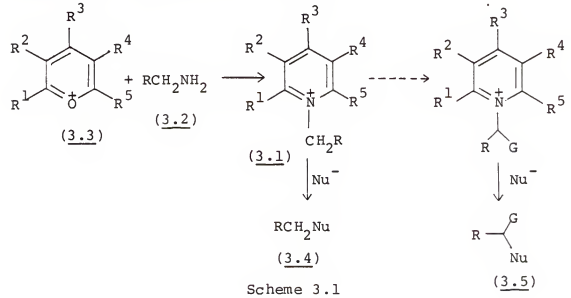
T.l.c. (silica gel; dichloromethane) showed then the absence of starting material. After cooling, ethanol was added slowly to destroy excess sodium hydride. Water was then added, the layers separated the aqueous layer extracted with dichloromethane, the organic layer washed with water and dried ($MgSO_4$). Evaporation of the solvents left a solid which after recrystallization from toluene afforded 0.54 g (30%) of product as yellow microcrystals, m.p. 214-215 ^{o}C. (Found: C, 90.68; H, 6.11; N, 3.28%. $C_{30}H_{23}N$ requires C, 90.68; H, 5.78; N, 3.52%); ν_{max} (cm^{-1}) ($CHBr_3$) 1590(m), 1565(m), 1490(m), 1445(m); δ (p.p.m.) ($CDCl_3$) 8.0 (2H, m), 7.8-7.2 (18H, m), 6.75 (1H, s), 5.0 (1H, d, J = 11 Hz), 2.1 (1H, d, J = 11 Hz); λ_{max} (ε) (CH_3CN) 348(16,666), 262(35,416); δ_c (p.p.m.) ($CDCl_3$) 149.13(s), 142.74(s), 141.38(s), 149.50(s), 139.33(s), 136.80(s), 131.53, 129.73, 128.85, 128.75, 128.36, 128.07, 127.83, 127.68, 127.05, 126.27, 125.88, 36.89(t); m/e (%) 397(97.11), 396(38.96), 295(31.90), 294(100), 217(19.12), 216(17.23), 215(46.32), 202(19.05), 91(39.45).

CHAPTER III
PYRIDINIUM YLIDES IN ALDOL
CONDENSATIONS AND MICHAEL ADDITIONS

3.1 Introduction

3.1.1 Pyridinium Ylides

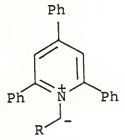
Pyridinium salts (3.1), made from primary amines (3.2) and pyrylium salts (3.3) (Scheme 3.1) are useful synthetic intermediates [for reviews see 80T679, 84AG(E)420]. Part of their usefulness resides in the fact that the heterocyclic ring can be replaced in nucleophilic substitution reactions by a large variety of nucleophiles (Scheme 3.1). The original amine is therefore converted into products (3.4) where the amino function has been replaced by other functionalities. Chapter II of this manuscript shows that the applicability of this method can be extended to hindered carbon nucleophiles and nitroamines.



Scheme 3.1

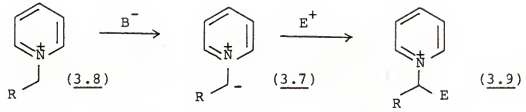
However, the synthetic utility of these compounds would be enhanced if functionality could be introduced at the α-position of the N-substituent before the nucleophilic displacement step. The products (3.5) obtained in this manner would be highly functionalized and the overall transformation, (3.2) to (3.5), would represent the α-functionalization of a primary amine followed by nucleophilic displacement of the amino group (Scheme 3.1).

Pyridinium ylides of the type (3.6) could serve in the realization of this program.



(3.6)

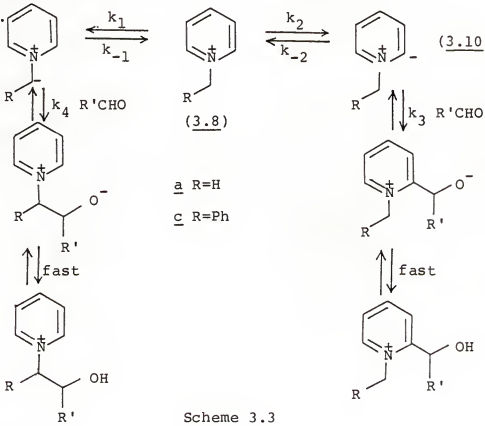
The classic work of Kröhnke [53AG605, 63AG(E)225] established that the pyridinium ylides (3.7) derived from N-methyl-, N-alkyl-, and N-benzyl-pyridinium salts (3.8) react with electrophiles to give synthetically useful adducts (3.9) (Scheme 3.2).



a R=H; b R=CH=CH$_2$; c R=Ph

Scheme 3.2

Interestingly, deuterium-hydrogen exchange studies [74CHE1] show that the exchange is faster at the H-2 and H-6 protons than at the α-CH$_2$ group of (3.8a) and (3.8c); yet, the reaction with electrophiles takes place exclusively at the α-CH$_2$ position. This has been explained by the equilibria shown in Scheme 3.3, where the relative rates were found to be $k_1 << k_{-1}$, $k_2 << k_{-2}$, $k_2 > k_1$ and $k_4/k_{-1} > k_3/k_{-2}$ [74CHE1].



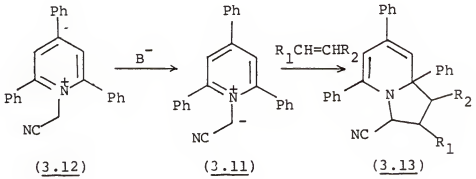
a R=H

c R=Ph

Scheme 3.3

If nucleophilic substitution reactions are to be performed on the adducts prepared from ylides, the 2-, 4-, and 6-positions of the pyridinium ring have to be substituted [80T679]. This prevents nucleophilic attack at those positions and (if the proper substituents are used) makes the pyridine moiety a good leaving group [80T679]. 2,4,6-Triphenylpyridinium salts (3.1); $R_1=R_3=R_5=Ph$) (Scheme 3.1) have been extensively used in nucleophilic displacement reactions [80T679, 84AG(E)420]. Some studies on ylides derived from these salts have been reported in the literature.

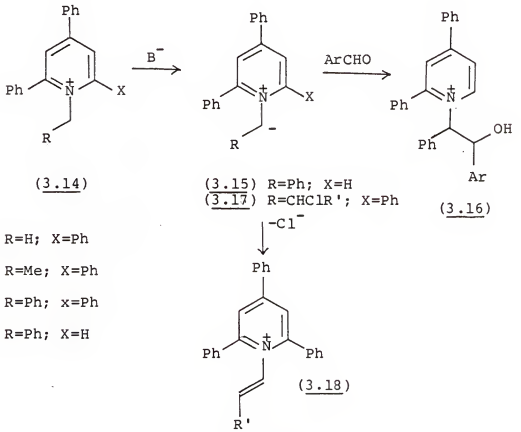
Thus, ylide (3.11), prepared from 1-cyanomethyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.12), was reacted with α,β-unsaturated carbonyl compounds to afford tetrahydroindolizines (3.13) (Scheme 3.4) [83H623].



(3.12) (3.11) (3.13)

Scheme 3.4

Attempts to generate the ylides from 1-methyl-, 1-ethyl-, and 1-benzyl-2,4,6-triphenylpyridinium salts (3.14) (Scheme 3.5) with LDA at -78 °C failed, presumably due to steric hindrance caused by the α,α'-diphenyl groups and/or to the insufficient stability of the ylide [81JO492]. It was found [81JO492], however, that a 10-fold excess of NaOH in a mixture of methanol and ethanol with 1-benzyl-2,4-diphenylpyridinium salt (3.14d) gave an equilibrium amount of the ylide (3.15), which could be trapped by aldehydes to afford adducts (3.16) (Scheme 3.5). Under similar conditions, the ylide (3.17) underwent loss of chloride anion to give N-vinylpyridinium salts (3.18) (Scheme 3.5) [82CS147].



(3.14)

(3.15) R=Ph; X=H
(3.17) R=CHClR'; X=Ph

(3.16)

a R=H; X=Ph

b R=Me; X=Ph

c R=Ph; x=Ph

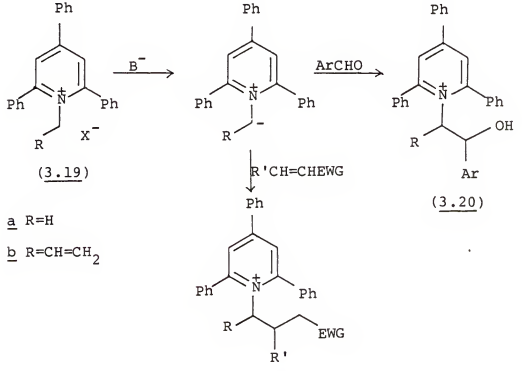
d R=Ph; X=H

(3.18)

Scheme 3.5

3.1.2 Aim of the Work

It was the purpose of the present work to generate pyridinium ylides from 1-methyl-(3.19a) and 1-allyl-2,4,6-triphenylpyridinium (3.19b) salts and trap them with aldehydes and Michael acceptors (Scheme 3.6)



(3.19)

a R=H

b R=CH=CH$_2$

(3.20)

Scheme 3.6

Previous work by Katritzky et al. [see 84J(PI)941] on 1-methyl-2,4,6-triphenylpyridinium trifluoromethanesulfonate (3.19a; X = CF_3SO_3) had shown that the use of 10 equivalents of NaOH and 5 equivalents of the aldehydes were necessary to form the adducts (3.20) (Scheme 3.6).

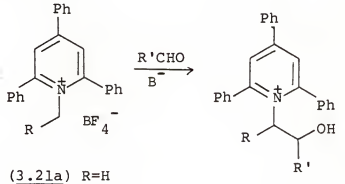
However, the conversion of (3.19a) into the adducts (3.20) was not complete under these conditions since starting material (3.19a) was always recovered. It was, thus, necessary to find better conditions under which to carry out the reactions and, if possible, to reduce the amount of base and aldehyde employed.

3.2 Results and Discussion

3.2.1 Reactions with Aldehydes

Preparation of adducts

1-Methyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.21a) was reacted with aromatic aldehydes in the presence of potassium t-butoxide in dimethyl sulfoxide at 20 °C for 24-30h (Table 3.1) to give the pyridinium ethanols (3.22) (Scheme 3.7) in good yields (Table 3.1). With the corresponding 1-allylpyridinium salt (3.21b) the yields and purity of the products depended considerably on the particular benzaldehyde used.



(3.21a) R=H (3.22) R=H

(3.21b) R=CH=CH$_2$ (3.23) R=CH=CH$_2$

Scheme 3.7

Table 3.1 Preparation of pyridinium ethanols (3.22) and (3.23)

Product no.	Starting aldehyde	Method[a]	Time (h)	Yield (%)	M.p. (°C)	Recryst. solvent	Crystal form	Required (%) C	Required (%) H	Required (%) N	Molecular formula	Found (%) C	Found (%) H	Found (%) N
(3.22a)	Benzaldehyde	B	30	73	195-197	EtOH	Plates	72.2	5.1	2.7	$C_{33}H_{26}BF_4NO$	71.8	5.0	2.7
(3.22b)	2-Chlorobenzaldehyde	B	24	87	188-190	EtOH	Needles	67.7	4.55	2.5	$C_{33}H_{25}BClF_4NO$	68.05	4.7	2.45
(3.22d)	3-Nitrobenzaldehyde	B	24	86	176-178	EtOH-Et_2O	Microcrystals	66.4	4.5	5.0	$C_{33}H_{25}BF_4N_2O_3$	66.6	4.6	5.0
(3.23a)	Benzaldehyde	A	48	46	94-96	Me_2CO-Et_2O	Prisms	73.2	5.2	2.6	$C_{33}H_{28}BClF_4NO$	73.5	5.3	2.7
(3.23b)	2-Chlorobenzaldehyde	A	16	60	132-135	Me_2CO-Et_2O	Microcrystals	68.8	4.7	2.4	$C_{33}H_{27}BClF_4NO$	68.7	4.7	2.4
(3.23c)	2-Nitrobenzaldehyde	A	26	67	114-116	CH_2Cl_2-Et_2O	Plates	67.6	4.6	4.8	$C_{33}H_{27}BF_4N_2O_3$	67.2	4.7	4.6
(3.23d)	3-Nitrobenzaldehyds	A	48	20	160-161	Me_2CO-Et_2O	Microcrystals	67.6	4.6	4.8	$C_{33}H_{27}BF_4N_2O_3$	67.5	4.6	4.5
		B	24	68[b]	157-159[c]	Me_2CO-Et_2O	Microcrystals	67.6	4.6	4.8	$C_{33}H_{27}BF_4N_2O_3$	67.4	4.6	4.6
(3.23e)	2-Methylbenzaldehyds	A	48	72	148-149	CH_2Cl_2-Et_2O	Prisms	73.5	5.4	2.5	$C_{34}H_{30}BF_4NO$	73.1	5.4	2.4

[a]For methods A and B see Experimental section. All compounds are tetrafluoroborate salts. [b]Yield of the mixture of diastereoisomers.
[c]One isomer after recrystallization.

The adducts (3.23) were conveniently prepared by allowing the pyridinium cation (3.21b) to react with the aldehyde and aqueous NaOH in a mixed methanol, ethanol and dichloromethane solvent at 0 ^{o}C over 15-48h (Table 3.1)(Scheme 3.7). A considerable excess of aldehyde (5 equivalents) was required to give good conversions in a reasonable reaction time; the yields still depended drastically on the substituents in the benzaldehydes. It appears that o-substitution gave consistently better yields than any other mono-substitution pattern in the benzaldehydes. The observation that p-chlorobenzaldehyde gave only a very poor yield of an adduct heavily contaminated with 1H-2,4,6-triphenylpyridinium tetrafluoroborate indicated that the effect was not electronic; the same substituent, when placed in the ortho position, gave a good yield of the corresponding adduct (3.23b). However, no consistent explanation can be offered at present to account for this behavior.

Formation of variable amounts of 1H-2,4,6-triphenylpyridinium tetrafluoroborate was also observed when attempts were made to recrystallize the adducts (3.23) from boiling ethanol. This result indicated that these compounds might be thermally unstable. The thermal behavior of both adducts (3.23) and (3.22) is discussed in Sections 3.2.3 and 3.2.4, respectively.

Spectroscopic properties of 1-(2-aryl-2-hydroxyethyl)-(3.22) and 1-(2-aryl-2-hydroxy-1-vinylethyl)-2,4,6-triphenylpyridinium (3.23) tetrafluoroborates

All adducts showed a medium to strong ν_{OH} absorption at ca. 3400 cm^{-1} in the i.r. spectra. The ^{1}H-n.m.r. spectra of the adducts (3.22) showed multiplets, due to the NCH_2CH protons, in the region 4.2-6.15 p.p.m. (Table 3.2).

The allylic protons of the 1-allylpyridinium salt (3.21b) resonate in the same region in the ^{1}H-n.m.r. spectrum as the olefinic and aliphatic protons of the adducts (3.23) (Table 3.2); therefore, this technique could not be used satisfactorily for their characterization. The ^{13}C-n.m.r. spectra were, however, more useful with two doublets [corresponding to the NCHCH(OH) carbons] observed in the region 69.2-76.3 p.p.m. (Table 3.3). The existence of diasteriomers also could be detected by this technique [e.g. in (3.23d)] (Table 3.3); the predominant isomer was separated by a simple recrystallization. All adducts gave satisfactory elemental (C,H,N) analyses.

Table 3.2 ^{1}H N.m.r. spectra of 1-(2-aryl-2-hydroxyethyl)(3.22) and 1-(2-aryl-2-hydroxy-1-vinylethyl)-2,4,6-triphenylpyridinium (3.23) tetrafluoroborates

Compound[a] no	R'	3,5-H 2 H (s) δ	δ	R' H	M	Other aromatic protons (m) δ	+NCHR- H	δ	H	M	-CH(OH)R 1H δ	M	-CH=CH$_2$ 3H δ	M
(3.22a)	C_6H_5	8.0	7.15	3	m	7.75	15	4.70	2	b[b]	4.70	b[b]		
			6.5	2	m									
(3.22b)	2-ClC_6H_4	8.05	7.1	4	m	7.7	15	5.3-4.2	2	m[b]	5.3-4.2	m[b]		
(3.22d)	3-$NO_2C_6H_4$	8.2		c		8.1-6.8	19	4.85	2	b[b]	4.85	b[b]		
(3.23a)	C_6H_5	c	7.2	3	m	8.3-7.4	17	6.1-4.4	1	m[b]	6.1-4.4	m[b]	6.1-4.4	m[b]
			6.75	2	m									
(3.23b)	2-ClC_6H_4	c	7.1	4	m	8.3-7.35	17	6.0-4.6	1	m[b]	6.0-4.6	m[b]	6.0-4.6	m[b]
(3.23c)	2-$NO_2C_6H_4$	8.15		c		8.1-7.1	19	6.0-4.3	1	m[b]	6.0-4.3	m[b]	6.0-4.3	m[b]
(3.23d)	3-$NO_2C_6H_4$	8.15		c		8.1-7.0	19	5.9-4.6	1	m[b]	5.9-4.6	m[b]	5.9-4.6	m[b]
(3.23e)[d]	2-MeC_6H_4	8.2	7.2-6.6	4	m	8.1-7.4	15	6.0-4.6	1	m[b]	6.0-4.6	m[b]	6.0-4.6	m[b]

[a]All spectra recorded in $CDCl_3$-CF_3CO_2H; δ=chemical shift (p.p.m.); J=coupling constant (Hz); H=number of protons, M=multiplicity, s=singlet, d=doublet, dd=double doublet, m=multiplet, b=broad singlet.
[b]Obscured by signals in the same region. [c]With rest of aromatic protons. [d]C-CH_3:δ 1.7 (3 H,s).

Table 3.3 ^{13}C N.m.r. chemical shifts of the aliphatic region on pyridinium ethanols (3.23)

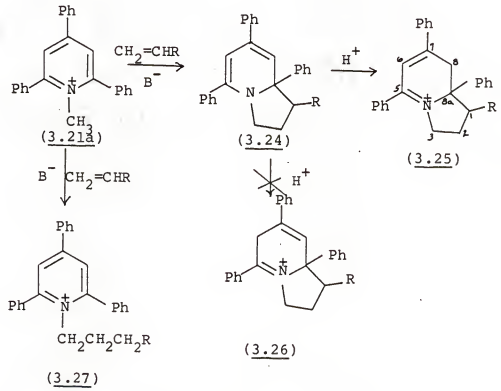
Compound[a] no	C-1' (d)	C-2' (d)
(3.23a)	74.0	74.4
(3.23b)	69.6	75.7
(3.23c)	68.0	76.3
(3.23d)	73.5	74.4
(3.23e)	69.2	75.8

[a]Spectra recorded in $CDCl_3$ TFA with $CDCl_3$ as internal reference, chemical shift in p.p.m. [b]The mixture of diastereoisomers showed also, C-1' at 73.1 and C-2' at 76.0. [c]2'-CH_3 (18.6 q).

3.2.2 Conjugate Addition to Acrylates

Formation of indolizine derivatives

The reaction between 1-methyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.21a) and acrylonitrile in the presence of potassium t-butoxide in t-butanol gave the tetrahydroindolizine (3.24a) (Scheme 3.8) which was characterized by ^{1}H-n.m.r. spectroscopy (vide infra).



a R=CN; b R=CO_2Me; c R=CO_2Et

Scheme 3.8

Upon treatment with fluoroboric acid, the tetrahydroindolizine (3.24a) was converted to the tetrahydroindolizinium tetrafluoroborate (3.25a) (Scheme 3.8) which was characterized according to its spectral (i.r., u.v., ^{1}H-, ^{13}C-n.m.r.) properties and elemental (C,H,N) analysis. In practice, the tetrahydroindolizinium salt (3.25a) was obtained without isolation of the intermediate tetrahydroindolizine (3.24a) by fluoroboric acid treatment during the work-up procedure.

Spectroscopic properties of 1-cyano-2,3,4,8a-tetrahydro-5,7,8a-triphenyl-1H-indolizine (3.24a) and 1-cyano-2,3,8,8a-tetrahydro-5,7,8a-triphenyl-1H-indolizinium tetrafluoroborate (3.25a)

In the ^{1}H-n.m.r. spectrum of (3.24a), the phenyl protons gave a multiplet at 7.8-7.1 p.p.m.; the 6-H and 8-H protons gave characteristic singlets at 6.0 and 5.8 p.p.m. [83H623]; the 3H and 1-H protons resonated as a multiplet at 3.8-3.3 p.p.m.; the remaining methylene 2-H protons appeared as a multiplet at 2.9-2.0 p.p.m.

The ^{1}H-n.m.r. spectrum of (3.25a) showed the 6-H as a singlet at 7.0 p.p.m.; the protons at position 3 gave a triplet (J = 7 Hz) at 4.5 p.p.m.; the H-1 and H-8 protons appeared as a multiplet at 4.2-3.8 p.p.m., as did the H-2 protons at 2.7-2.3 p.p.m. The ^{13}C-n.m.r. spectrum of (3.25a) provided additional confirmation of the tetrahydroindolizinium structure showing quaternary olefinic carbons C-5 and C-7 as singlets at 173.20 and 161.21 p.p.m., respectively; C-6 gave a doublet at 124.22 p.p.m. The aromatic carbons appeared between 135.43 and 124.22 p.p.m. In the aliphatic region,

C-8a gave a singlet at 73.34 p.p.m., C-1 a doublet at 42.44 p.p.m., while C-3, C-8 and C-2 gave triplets at 54.09, 36.84 and 28.01 p.p.m., respectively.

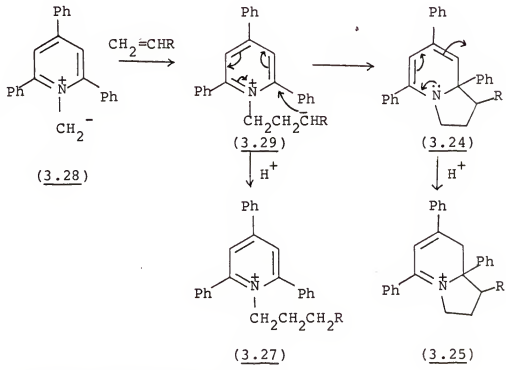
The u.v. spectrum of (3.25a) shows two maxima at 241.7 (ε = 15120) and 361.4 (ε = 8975) mm, confirming that protonation of the tetrahydroindolizine (3.24a) has taken place at the 8- position. If protonation had taken place at the 6-position, the resulting tetrahydroindolizinium salt (3.26a) (Scheme 3.8) would have shown only styrene-type absorptions (λ_{max} ca. 244; ε ca. 12000) [72CR1, 83JA1204].

Mechanism of formation

The formation of tetrahydroindolizines from pyridinium ylides, upon reaction with activated olefins, is well documented in the literature [80J(PI)1180, 83H623]. However, it was found [82TH155, 84J(PI)941] that the reaction of 1-methyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.21a) with methyl acrylate and sodium methoxide gave a mixture of the Michael adduct (3.27b) and the tetrahydroindolizinium tetrafluoroborate (3.25b). A similar reaction with ethyl acrylate and sodium ethoxide gave only the Michael adduct (3.27c) (Scheme 3.8).

The cyclized products (3.25a) and (3.25b) could possibly be formed by a concerted 1,3-dipolar cycloaddition [63AG604]. However, as the formation of (3.27b) and (3.27c) indicates, it is more probable that the pyridinium ylide (3.28) (Scheme 3.9) undergoes a Michael addition onto the activated olefin giving a carbanionic intermediate (3.29); this is then either

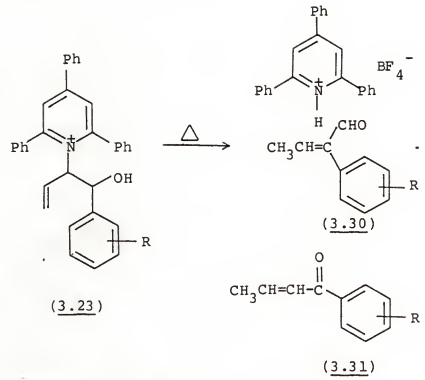
protonated or cyclized to the pyridinium ring giving the observed products.



Scheme 3.9

3.2.3. Thermolysis of the Adducts (3.23)

The adducts (3.23b) and (3.23d), when heated under reflux in chlorobenzene for 2h, gave 1H-2,4,6-triphenylpyridinium tetrafluoroborate, together with the crotonaldehydes (3.30b) and (3.30d), and the isomeric aryl propenyl ketones (3.31) (Scheme 3.10).



(3.23)

(3.30)

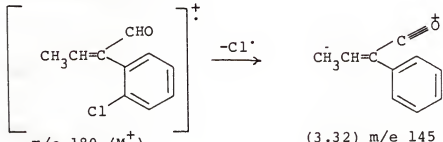
(3.31)

b R=2-Cl; d R=3-NO_2; e R=2-Me

Scheme 3.10

The product ratios (3.30b):(3.31b) and (3.30d):(3.31d) were 80:20 and 46:54, respectively, as judged by the ^{1}H-n.m.r. ratios of the aldehyde protons to the total C-Me peak areas. The ^{13}C-n.m.r. and g.c./mass spectral results confirmed the presence of the two compounds. Thus, the ^{13}C-n.m.r. spectrum of the mixture of (3.30b) and (3.31b) showed two methyl carbons at 15.5 and 18.2 p.p.m.; the aldehyde carbonyl carbon gave a doublet at 191.7 p.p.m.

The mass spectrum of crotonaldehyde (3.30b) (Scheme 3.11) showed a weak molecular ion at m/e 180. The main fragmentation was a loss of Cl· to give the base peak (3.32) at m/e 145 which lost CO and two H· to form the acetylenic fragment (3.33) (m/e 115).



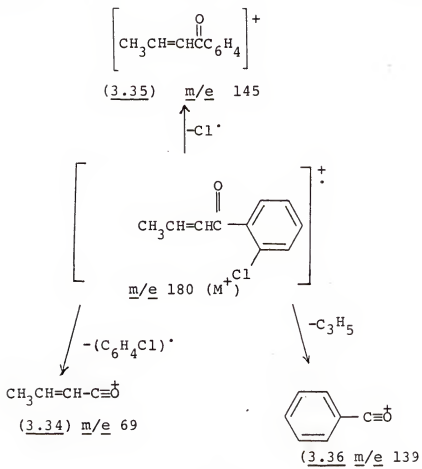
m/e 180 (M^+)

(3.32) m/e 145

(3.33) m/e 115

Scheme 3.11

The mass spectrum of the ketone (3.31b) (Scheme 3.12) also showed a weak moleuclar ion at m/e 180. The base peak (3.34) (m/e 69) originated from the loss of a chlorophenyl radical. The other prominent peaks originated from the loss of Cl· from the molecular ion to give (3.35) (m/e 145) and from the loss of C_3H_5 to form the acyl cation (3.36) (m/e 139).



Scheme 3.12

The thermolysis of (3.23b) also gave traces of o-chlorobenzaldehyde, identified by g.c./mass spectroscopy. Other unidentified products were formed from (3.23d).

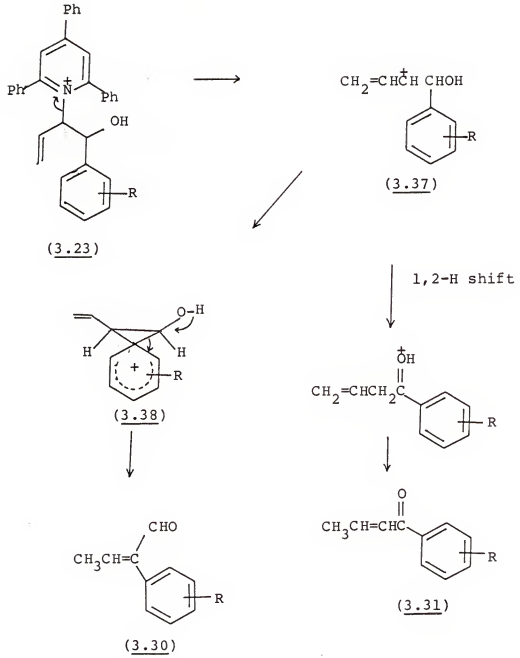
The thermolysis of (3.23e) gave the crotonaldehyde (3.30e) (Scheme 3.10) with the expected ^{1}H- and ^{13}C-n.m.r. spectra (see Experimental section). Traces of the ketone (3.31e) (Scheme 3.10) were detected in the product mixture by g.c./mass spectroscopy.

Mechanism of thermolysis

The formation of the ketones (3.31) and aldehydes (3.30) can be explained by a 1,2-H or -aryl shift on the allylic carbenium ion (3.37), followed by proton loss and isomerization of the double bond (Scheme 3.13).

The different ratios of aldehydes and ketones reflect the different migratory aptitudes of the aryl groups [77MI971]. Thus, the stabilizing effect of the methyl group on the intermediate phenonium ion (3.38e) (Scheme 3.13) [70JA5244] results in the almost exclusive formation of the aldehyde (3.30e). Chloro-substitution on the migrating aryl group stabilizes the phenonium ion (3.38b) less efficiently than a methyl group does and this is reflected in the formation of a significant amount of the ketone (3.31b). The destabilizing effect of the nitro group on (3.38d) results in predominant formation of the ketone (3.31d) (Scheme 3.13).

The presence of the substituted benzaldehydes in the thermolysis products results from the retro-condensation of adducts (3.23). This is the favored process in the thermolysis of the unsubstituted pyridinium ethanols (3.9) [35CB1935].

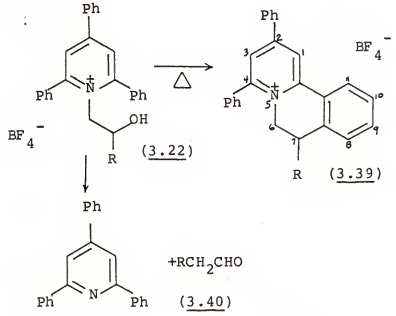


b R=2-Cl; d R=3-NO_2; e R=2-Me

Scheme 3.13

3.2.4 Thermolysis of the Adducts (3.22)

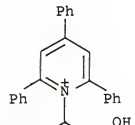
The pyridinium ethanol (3.22b) (Scheme 3.14) was unaffected when heated at reflux in chlorobenzene, but at 220-230 °C, in the absence of solvent, gave the tetrahydroquinolizinium salt (3.39b) in 25% yield. Similarly, the benzaldehyde derivative (3.22a) gave (3.39a) in 54% yield (Scheme 3.14). However, on thermolysis the adduct (3.22d) underwent considerable decomposition to give a tar.



a R=Ph; b R=2-ClC_6H_4; d R=3-$NO_2C_6H_4$

Scheme 3.14

In all cases, 2,4,6-triphenylpyridine was also formed, probably by loss of the aldehydes (3.40) formed by 1,2 - aryl migration. A similar 1,2-hydrogen migration had been reported in the formation of aldehydes from hydroxy-alkyl pyridinium salts (3.41) (Scheme 3.15) [81T2383].



(3.41)

Scheme 3.15

The quinolizinium salts (3.39) were characterized by their elemental (C,H,N) analyses and spectral (i.r., ^{1}H-, and ^{13}C-n.m.r.) properties.

Spectroscopic properties of 6,7-dihydro-2,4,7-triaryl-benzo[a]quinolizinium tetrafluoroborates (3.39)

The i.r. spectra of salts (3.39) show the absence of hydroxyl group absorption. The presence of bands at 1625 and 1050 cm^{-1} confirms the pyridinium-like structure and the tetrafluoroborate anion, respectively.

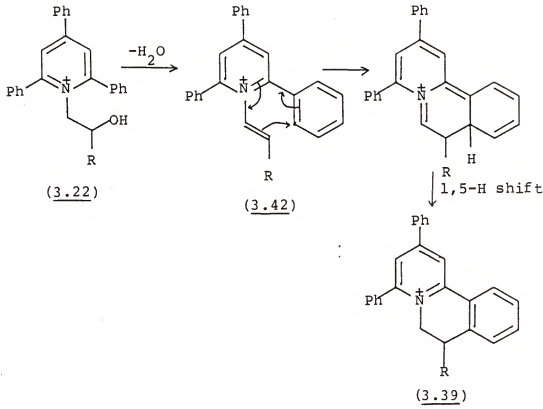
The main feature of their ^{1}H-n.m.r. spectra is the evidence for an unsymmetrical structure; thus, H-1 gives doublets at 8.8 (J = 2 Hz) and 8.7 p.p.m. for (3.39a) and (3.39b), respectively. This contrasts with the singlets (2H) at

8.0 p.p.m. given by the β-protons in the pyridinium ethanols (3.22) (Table 3.2). H-3 resonates with the bulk of the aromatic protons. The aliphatic protons appear as multiplets in the region 5.3-4.3 p.p.m.

The ^{13}C-n.m.r. spectra of (3.39) show two different pyridinium α-carbons and the γ-carbon in the region 155.2-149.0 p.p.m.; the C-6 carbons gave triplets at 55.6 and 53.6 p.p.m., and the C-7 carbons gave doublets at 40.8 and 38.4 p.p.m., for (3.39a) and (3.39b), respectively.

Mechanism of formation of quinolizinium salts (3.39)

The formation of these products can be explained by a two-step process involving dehydration of the adducts (3.22) followed by a [4n + 2] electrocyclic ring closure and a 1,5-hydrogen shift (Scheme 3.16). Support for this mechanism was found upon examination of the ^{1}H-n.m.r. spectrum of the mother liquors from the recrystallization of the product mixture from the thermolysis of (3.23b); this showed the presence of residual (3.39b) and another pyridinium salt that contained only aromatic protons; the significant feature of its ^{1}H-n.m.r. spectrum was that the β-protons resonated as a sharp singlet at 8.2 p.p.m., typical of 2,4,6-triphenyl-pyridinium salts (*vide supra*). On these bases, the product was assigned the structure of the vinylpyridinium salt (3.42b) (Scheme 3.16). The presence of (3.42b) in the reaction mixture suggested that (3.42b) could be an intermediate in the formation of (3.39b).

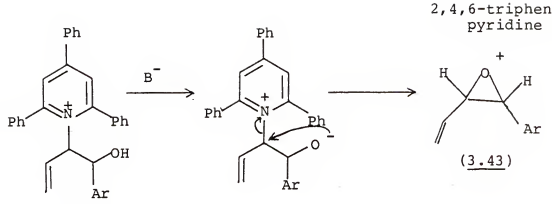


a R=Ph; b R=2-ClC_6H_4

Scheme 3.16

3.2.5 Treatment of Adducts (3.23) with Base

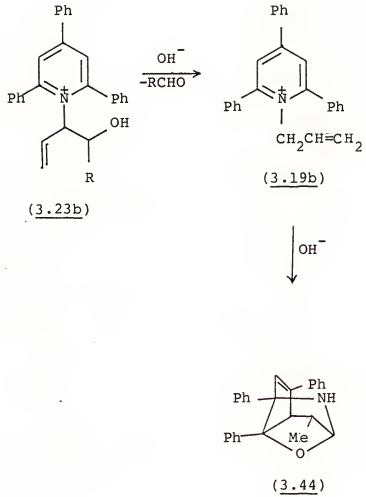
The presence of a pyridine leaving group adjacent to a hydroxyl group in adducts (3.22) and (3.23) offered the possibility of epoxide formation [73MI187]. The presence of the vinyl group in adducts (3.23) was particularly attractive since these compounds could give functionalized epoxides (3.43) (Scheme 3.17).



(3.23) (3.43)

Scheme 3.17

However, when the adduct (3.23b) was stirred at room temperature for 18h with excess sodium hydroxide in a mixed water, methanol, ethanol and dichloromethane solvent, very little of the expected 2,4,6-triphenyl pyridine was formed (Scheme 3.17), as shown by ^{1}H-n.m.r. spectroscopy. Instead, (3.23b) underwent a retro-aldol condensation reaction to form the 1-allyl-2,4,6-triphenylpyridinium salt (3.19b). This compound, then, underwent base attack and rearrangement to give the cage compounds (3.44) (Scheme 3.18) as reported in the literature [84JO448]. Compounds (3.44) were identified by comparison of the ^{1}H-n.m.r. spectrum of the mixture with the corresponding spectrum of authentic materials [82TH100].



(3.23b) (3.19b) (3.44)

Scheme 3.18

The treatment of (3.23b) with potassium t-butoxide in refluxing THF or DMSO at 60 °C led to the formation of complex mixtures, as shown by t.l.c., that were not separated. The ^{1}H-n.m.r. spectra of the crude mixtures could not be interpreted.

3.3 Conclusions

1-Methyl-and 1-allyl-2,4,6-triphenylpyridinium salts react, through the corresponding ylides, with aromatic aldehydes at the α-CH_2 to give aldol products in good yields. While the 1-allyl adducts require a considerable excess of NaOH (12 equivalents) and aldehyde (5 equivalents) to obtain good conversions, the 1-methyl adducts were formed with a moderate (2 equivalents) excess of aldehyde in the presence of potassium t-butoxide.

1-Methyl-2,4,6-triphenylpyridinium tetrafluoroborate reacted with acrylonitrile under basic conditions to give, after acidic work-up, 1-cyano-2,3,8,8a-tetrahydro-5,7,8a-triphenyl-1H-indolizinium tetrafluoroborate. The reaction was shown to involve a Michael addition of the corresponding ylide to the olefin.

The allyl adducts were thermally converted into mixtures of crotonaldehydes and α,β-unsaturated ketones. The ratio of aldehyde to ketone formed depended on the aryl substituent that was introduced with the original benzaldehyde.

The aldol adducts derived from 1-methyl-2,4,6-triphenylpyridinium tetrafluoroborate gave on thermolysis 2,4,7-triaryl-6,7-dihydrobenzo[a]quinolizinium tetrafluoroborates. The intermediate formation of 1-styryl-2,4,6-triphenylpyridinium derivatives was proposed.

3.4 Experimental

For general instrumental details see Section 2.4.

Dimethyl sulfoxide (DMSO) was distilled from calcium hydride and stored over 4Å molecular sieves. Tetrahydrofuran (THF) was dried by refluxing over sodium with benzophenone as indicator.

The following compounds were prepared by reported methods: 2,4,6-triphenylpyrylium tetrafluoroborate (3.3; R_1=R_3=R_5=Ph; R_2=R_4=H) (45%), m.p. 225-232 °C (lit. [58BSF1458] m.p. 232-234 °C); 1-methyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.21a) (84%), m.p. 217-220 °C (lit. [79J(PI)430] m.p. 215-216 °C); 1-allyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.21b) (76%), m.p. 164-166 °C (lit. [79J(PI)2501] m.p. 169-170 °C).

3.4.1 Reactions with Aldehydes

Method A

To the pyridinium salt (3.21b) (1 mmol) and the aldehyde (5 mmol) in ethanol (6 ml), methanol (6 ml), and dichloromethane (4.8 ml) at 0 °C, NaOH (10 M; 1.2 ml) was added, with occasional stirring, and the solution was kept at 0 °C for the appropriate time (Table 3.1). The solution was acidified with glacial acetic acid, the solvent removed (20 °C/10 mmHg) and the residue extracted with dichloromethane (2 x 20 ml). An excess of fluoroboric acid (48%) was added to the organic extracts, which were then washed with water and dried over $MgSO_4$. The solvent was removed (20 °C/10 mmHg) and the

residue was washed and triturated with diethyl ether until crystallization of the adducts (3.23) took place.

Method B

Potassium t-butoxide (1.4 mmol) was added in portions to a stirred solution of the pyridinium salt (3.21a) or (3.21b) (1 mmol) and the aldehyde (2 mmol) in dry DMSO (8 ml) at 20 °C, and the reaction mixture was stirred at 20 °C for the appropriate time (Table 3.1). It was then poured into ice and extracted with dichloromethane (2 x 25 ml). The extracts were washed with water, the solvent evaporated, and the residue dissolved in diethyl ether and filtered. Addition of an excess of fluoroboric acid (48%) to the filtrate afforded the crystalline adducts.

3.4.2 Michael Addition

Preparation of 1-cyano-2,3,8,8a-tetrahydro-5,7,8a-triphenyl-1H-indolizinium tetrafluoroborate (3.25a)

To stirred potassium t-butoxide (0.164g, 1.5 mmol) in t-butanol (20 ml) was added 1-methyl-2,4,6-triphenylpyridinium tetrafluoroborate (3.21a) (0.5g, 1.2 mmol). The mixture was stirred for 15 min. and then acrylonitrile (0.064g, 1.2 mmol) in t-butanol (5 ml) was added dropwise. The reaction mixture was then refluxed for 2h. As it cooled, inorganic material separated and was filtered off; fluoroboric acid (48%, excess) was then added to the filtrate. Addition of diethyl ether to the mixture gave a precipitate which was collected after it had been stirred at room temperature for 12h

(0.3g, 53%); on crystallization from absolute ethanol it formed yellow prisms, m.p. 181-183 °C (Found: C, 70.13; H, 5.02; N, 6.05. $C_{27}H_{23}BF_4N_2$ requires C, 70.16; H, 4.98; N, 6.06%); ν_{max} (cm^{-1}) ($CHBr_3$) 1610(s) and 1050(s,b); δ (p.p.m.) ($CDCl_3$-TFA) 2.7 (2H, m), 3.8-4.2 (3H, m), 4.5 (2H, t, J = 7 Hz), and 7.1-8.2 (16H, m); λ_{max} (mm) (MeOH)(ε) 242 (15,120) and 361 (8,980); δ_C (p.p.m.) ($CDCl_3$-TFA) 28.01(t), 36.84(t), 42.44(d), 54.09(t), 73.34(s), 118.32(d), 124.22-135.43 (aromatic-C), 161.21(s), and 173.20(s).

3.4.3 Thermolysis Reactions

General procedure for the thermolysis of the adducts (3.23)

The pyridinium ethanol (3.23) (5 mmol) was refluxed with stirring in chlorobenzene (50 ml) for 1.5-2h., after which the mixture was cooled and ether added to precipitate 1H-2,4,6-triphenylpyridinium tetrafluoroborate. The solvent was removed under reduced pressure (50 °C/20 mmHg) and diethyl ether added to the residue; fluoroboric acid (48%, excess) was added to the stirred suspension to precipitate the remaining 2,4,6-triphenylpyridine. After filtration, the solution was washed with water (20 ml), the organic layer dried ($MgSO_4$), the solvent evaporated, and the remaining oil distilled under reduced pressure.

The thermolysis of (3.23b) gave 2-(2-chlorophenyl)but-2-enal (3.30b), 2-chlorophenylprop-1-enyl ketone (3.31b) and 2-chlorobenzaldehyde (traces) in 56% yield; b.p. 80 °C/0.7 mmHg; ν_{max} (cm^{-1}) (neat) 1690(s) and 1640(m); δ (p.p.m.)

($CDCl_3$) 1.85 [d, CH_3-C=, (3.30b), (3.31b], 7.6-6.5 (aromatic-H), and 9.8 (s, CHO); δ_C (p.p.m.) ($CDCl_3$) 15.57 [q, (3.30b)], 18.20 [q, (3.31b)], 126.37(d), 129.12(d), 130.93(d), 143.10(s), 147.67(d), 152.05(d), and 191.72(d, CHO). The ratio (3.30b):(3.31b) was 80:20, G.c./mass spectroscopy, m/e (%) for (3.30b) 182(1.6), 180(4.7), 145(100), 117(28.8), 116(47.1), 115(70.9), 89(12.7), 75(8.7), 63(16) and 39(19.9); m/e (%) for (3.31b) 182(4.1), 180(11.9), 145(39.1), 141(14.1), 139(51.5), 113(7.2), 111(20.3), 75(21.8), 69(100), and 41(41.9).

The thermolysis of (3.23d) gave 2-(3-nitrophenyl)but-2-enal (3.30d) and 3-nitrophenylprop-1-phenyl ketone (3.31d) together with unidentified products; b.p. 160 ^{o}C/3.5 mmHg; ν_{max} (cm^{-1}) (neat) 1690(s), 1675(s), 1620(s), 1530(s), and 1350(s); δ (p.p.m.) ($CDCl_3$) 2.05 [CH_3-C= (3.30d), (3.31d)], 8.9-6.8 (aromatic-H), and 9.8 (s, CHO). The ratio (3.30d):(3.31d) was 46:54. The mixture could not be separated by g.c./mass spectroscopy.

From the thermolysis of (3.23e), 2-(2-methylphenyl)but-2-enal (3.30e) was obtained in 61% yield; b.p. 176-178 ^{o}C/2.2 mmHg; ν_{max} (cm^{-1}) ($CHBr_3$) 1690(s) and 1630(m); δ (p.p.m.) ($CDCl_3$) 1.8 (d, 3H, J 7 Hz), 2.1 (s, 3H), 6.7-7.4 (m, 5H), and 9.7 (s, 1H); δ_C (p.p.m.) ($CDCl_3$) 15.64(q, CH_3C=), 19.34 (q, CH_3-Ar), 125.49(d), 127.97(d), 129.34(d), 129.87(d), 132.31(s), 136.21(s), 145.62(s), 151.37(d) and 192.99(d, CHO). Found: M^+, 160.0879. Calculated for $C_{11}H_{12}O$: M^+, 160.0888.

General procedure for the thermolysis of the adducts (3.22)

The pyridinium ethanol (3.22) (1 mmol) was heated neat at 230 °C for 20-60 min. On cooling the residue was triturated with diethyl ether, until crystallization occurred.

6,7-Dihydro-2,4,7-triphenylbenzo[a]quinolizinium tetrafluoroborate (3.39a) was obtained from (3.22a) in 54% yield (time 60 min.), m.p. 141-144 °C, needles (from acetone-diethyl ether) (Found: C, 74.94; H, 4.89; N, 2.81. $C_{31}H_{24}BF_4N$ requires C, 74.87; H, 4.83; N, 2.81%); ν_{max} (cm^{-1}) ($CHBr_3$) 1625(s) and 1050(s,b); δ (p.p.m.) ($CDCl_3$-TFA) 4.3-5.1 (3H, m), 6.7-8.4 (19H, m), 8.5 (1H, m) and 8.8 (1H, d, J = 2 Hz); δ_C (p.p.m.) [$(CD_3)_2SO$] 40.86 (d, C-7), 55.63 (t, C-6), and 120.59-155.25 (aromatic-C).

7-(2-Chlorophenyl)-6,7-dihydro-2,4-diphenylbenzo[a]quinolizinium tetrafluoroborate (3.39b) was prepared from (3.22b) in 25% yield (time 20 min.), m.p. 268-270 °C, needles (from ethanol) (Found: C, 69.65; H, 4.30; N, 2.45. $C_{31}H_{23}BClF_4N$ requires C, 70.01; H, 4.32; N, 2.63%); ν_{max} (cm^{-1}) ($CHBr_3$) 1625(s) and 1050(s,b); δ (p.p.m.) [$(CD_3)_2SO$] 4.4-5.4 (3H, m), 6.7-7.10 (1H, m), 7.1-8.1 (14H, m), 8.4 (3H, m), 8.85 (1H, m) and 9.15 (1H, bs); δ_C (p.p.m.) [$(CD_3)_2SO$] 38.42(d, C-7), 53.63(t, C-6), and 120.79-155.25 (aromatic-C).

CHAPTER IV
LITHIO-DERIVATIVES STABILIZED BY HETEROCYCLES

4.1 Introduction

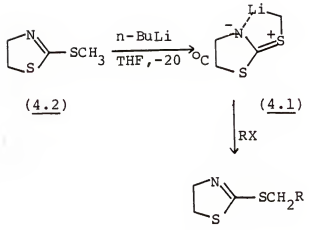
Heterocyclic systems can be used to stabilize carbanions in different ways. Chapter III of this dissertation (and references cited therein) shows the usefulness of pyridinium ylides in carbanionic reactions.

4.1.1 Dipole Stabilized Carbanions

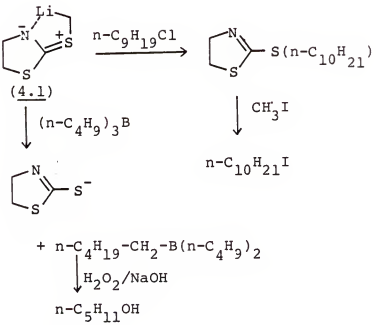
Dipole stabilized carbanions where the dipole is part of a heterocyclic system have found useful synthetic applications [for reviews see 78CR275, 80OR1]. Some of them are summarized here.

Thus, the organolithium (4.1), which is formally a dipole stabilized carbanion, was generated by metallation of 2-methylthiothiazoline (4.2) and could be trapped by alkyl halides (Scheme 4.1) [74H185].

Derivatives of (4.1) can be converted to alkyl iodides [74H185] and alcohols [75JO814] (Scheme 4.2).

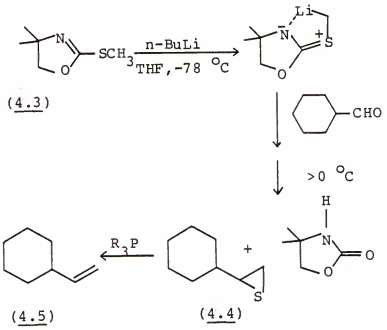


Scheme 4.1



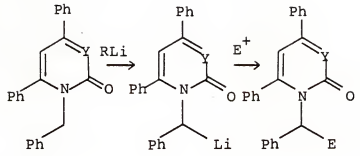
Scheme 4.2

The analogous oxazoline derivatives (4.3) has been used to produce thiiranes (4.4), which can themselves be converted to olefins (4.5) (Scheme 4.3) [76JO1735, 76S413].



Scheme 4.3

The amido functionality, extensively used by Beak and others [78CR275] in acyclic compounds, has also found applications in heterocyclic systems. Thus, the N-benzylpyridone (4.6) and N-benzylpyrimidone (4.7) undergo lithiation and subsequent reactions with carbonyl compounds, as shown in Scheme 4.4 [80J(PI)2851, 82J(PI)153].

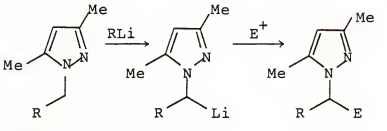


(4.6) Y=CH

(4.7) Y=N

Scheme 4.4

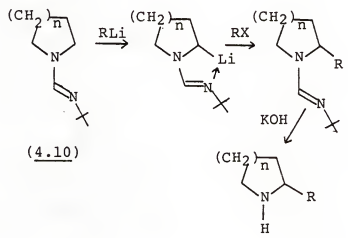
The α-position of 1-alkyl-3,5-dimethylpyrazoles (4.8) has been metallated and the lithio-derivatives (4.9) trapped by a variety of electrophiles (Scheme 4.5) [83T2023].



(4.8) (4.9)

Scheme 4.5

Very recently [84JA3270, 85JO1019] the work of Meyers et al. has developed the use of formamidines (4.10) as α-metallo amine synthetic equivalents (Scheme 4.6).

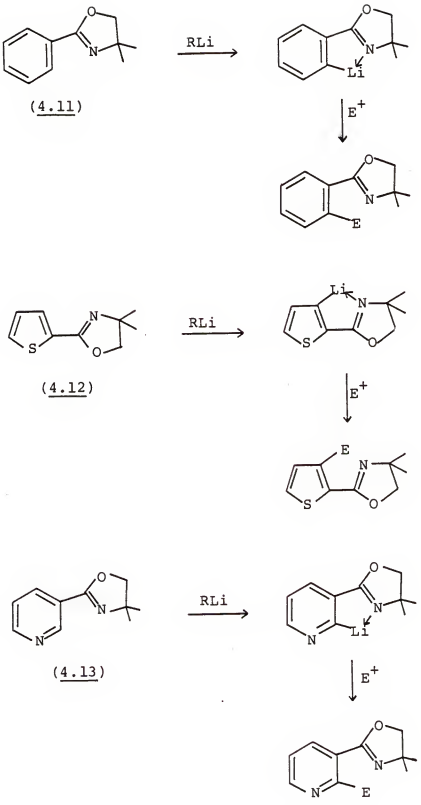


(4.10)

Scheme 4.6

4.1.2 Ortho Lithiation

Heterocycles have also been used in the ortho-directed lithiation of aromatic compounds [for a review on ortho lithiations see 79OR1]. The use of oxazolines in this field has been very recently reviewed [85T837]. Homo- (4.11) and hetero-aromatic (4.12, 4.13) compounds have been successfully ortho-lithiated by this method, as shown in Scheme 4.7. The effect of the heteroatom in directing the lithiation to the ortho position has been termed the "coordination only" mechanism [79OR1].

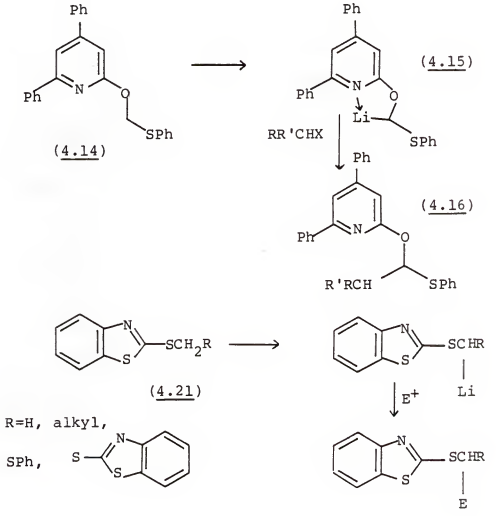


(4.11) (4.12) (4.13)

Scheme 4.7

4.1.3 Aim of the Work

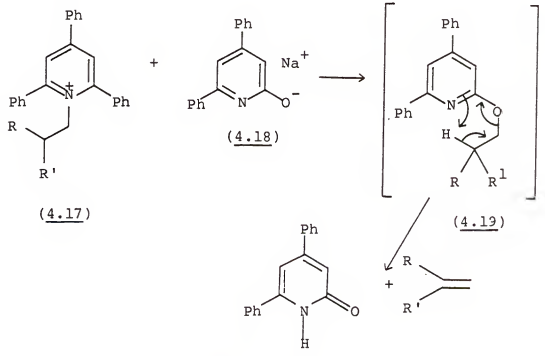
It was intended to study the formation (and further reaction with electrophiles) of carbanionic species stabilized by heteorcycles, by either dipole stabilization or a "coordination only" mechanism. Further manipulation of the heterocyclic moiety would give functionalized derivatives. The systems chosen for the study are shown in Scheme 4.8. A brief discussion on each of them is given now.



Scheme 4.8

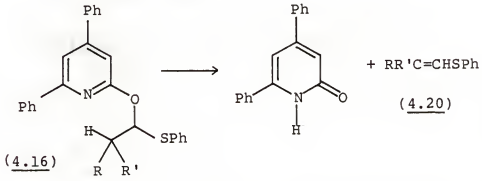
2-Alkoxypyridines

Stable carbanions alpha to oxygen are not easy to form [78CR275]. Therefore, the presence of the phenylsulphenyl group in (4.14) was considered necessary in order to provide further stabilization for the corresponding carbanion (4.15). The interest for the compounds (4.16) derived from (4.15) was aroused after Katritzky et al. reported that elimination reactions on pyridinium salts (4.17) were promoted by sodium 2-oxido-4,6-diphenylpyridine (4.18) (Scheme 4.9) [83MI85]. The reactions were thought to proceed through the intermediacy of the O-alkylated compounds (4.19) (Scheme 4.9) which underwent an elimination reaction analogous to the ester pyrolysis. 2-Alkoxypyridines are known to undergo this type of elimination [74S707, 82J(PII)1175].



Scheme 4.9

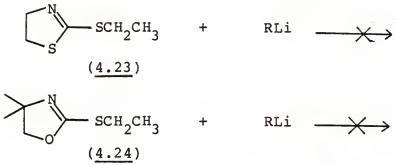
A similar elimination reaction on the compounds (4.16) would lead to enolthioethers (4.20) (Scheme 4.10) which are synthetically useful intermediates [see 83JA5075]. The overall transformation would represent the conversion of an alkyl halide RR'CHX into an enolthioether RR'C=CHSPh (Scheme 4.10).



Scheme 4.10

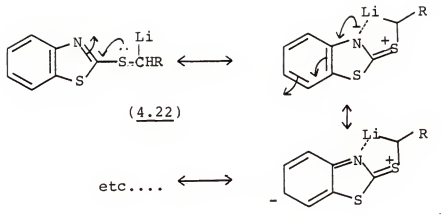
2-Alkylthiobenzothiazoles

One problem frequently encountered in some dipole stabilized carbanions adjacent to sulfur is the resistance of ethyl- and higher alkyl-derivatives to undergo lithiation under the usual conditions. Failures have been reported with the thiazoline [74H185] and oxazoline [76JO1735] systems, among others [75TL2865] (Scheme 4.11).



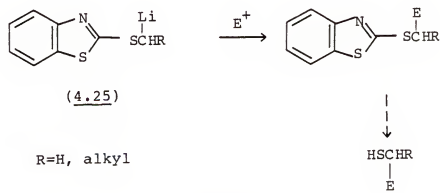
Scheme 4.11

In the 2-alkylthiobenzothiazole compounds (4.21) the presence of the benzene ring could be expected to afford further stabilization of the dipolar resonance structure (4.22) by delocalization of the negative charge (Scheme 4.12). As a consequence, when compared with (4.23) and (4.24) (Scheme 4.11), the benzothiazoles (4.21) would provide a more efficient stabilization of the corresponding lithio-derivatives.



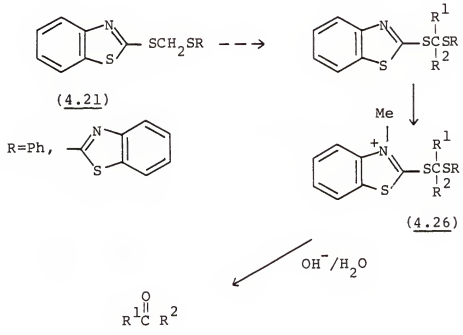
Scheme 4.12

2-Alkylthiobenzothiazole derivatives (4.21; R=H, alkyl) afford alkanethiols in a two step sequence [84TL2675]; this, combined with the reaction of (4.25) (Scheme 4.13) with electrophiles would produce secondary-alkyl thiols by formation of a C-C bond.



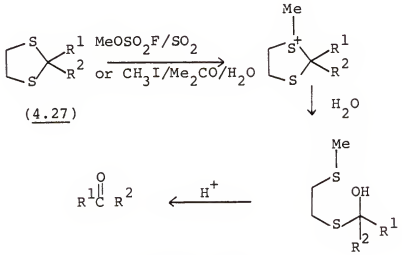
Scheme 4.13

The introduction of a second thio-substituent on the α-carbon, as in (4.21; R=Ph, benzothiazol-2-yl)(Scheme 4.14) offered other interesting synthetic possibilities. Dithio-derivatives (especially 1,3-dithianes) have been extensively used in synthesis as acyl anion equivalents [79AG(E)239, 79MI1]. However, the hydrolysis to the corresponding carbonyl compounds involves the use of undesirable mercuric salts in most cases and it is not always a successful reaction [71JO3553]. The system (4.21) (Scheme 4.14) offers the alternative of quaternization at nitrogen to give a salt (4.26) that should be easily hydrolyzed under mildly basic conditions (Scheme 4.14).



Scheme 4.14

A similar method has been reported in the literature for the cleavage of 1,3-dithiolanes (4.27) (Scheme 4.15) [72CC382]. The method, however, has not found general application since 2-lithio-1,3-dithiolanes are not stable enough to react efficiently with electrophiles [75JO231].

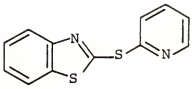


(4.27)

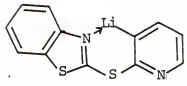
Scheme 4.15

Ortho-directed lithiation

It was interesting to test the possibilities of the benzothiazol-2-ylthio moiety as an ortho-directing group in the lithiation of heteroaromatic substrates. The 2-substituted pyridine (4.28) was chosen as a target for this study (Scheme 4.16).



(4.28)



Scheme 4.16

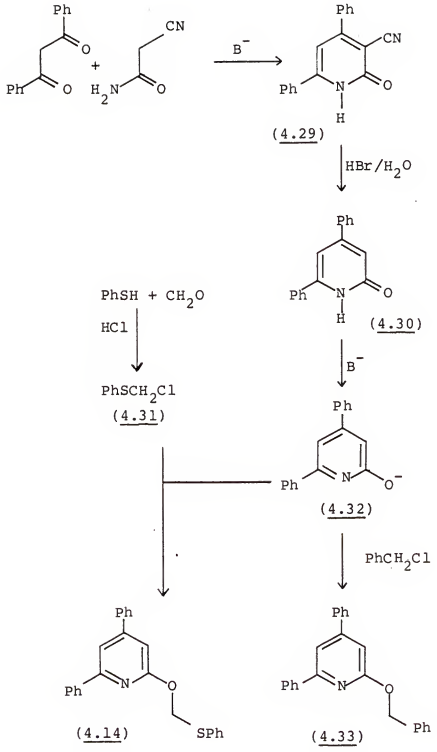
4.2 Results and Discussion

4.2.1 2-Alkoxypyridine Derivatives

Preparation of the 2-alkoxypyridine (4.14)

The synthesis of 4,6-diphenyl-2-(phenylthiomethoxy)-pyridine (4.14), required for the lithiation studies, was accomplished following the route described in Scheme 4.17.

3-Cyano-4,6-diphenyl-2-pyridone (4.29) was prepared according to a literature procedure [30JIC481]. Refluxing (4.29) in 48% hydrobromic acid gave an 80% yield of


Ph
O
Ph
O
CN
+
H_2N
O
B^-
Ph
CN
Ph
N
H
O
(4.29)
HBr/H_2O
Ph
Ph
N
H
O
(4.30)
PhSH + CH_2O
HCl
$PhSCH_2Cl$
(4.31)
B^-
Ph
Ph
N
O^-
(4.32)
$PhCH_2Cl$
Ph
Ph
N
O
SPh
(4.14)
Ph
Ph
N
O
Ph
(4.33)

Scheme 4.17

4,6-diphenyl-2-pyridone (4.30) (Scheme 4.17); this was characterized by its melting point [30JIC481] and spectral (i.r., ^{1}H-n.m.r.) characteristics (see Experimental section). Phenylthiomethyl chloride (4.31) was prepared in 71% yield following a method described in the literature for arylthiomethyl chlorides (Scheme 4.17) [62CA11499]; its boiling point was in agreement with the value reported in the literature [74JO2648]. The ^{1}H- and ^{13}C-n.m.r spectra confirmed the structure (see Experimental section).

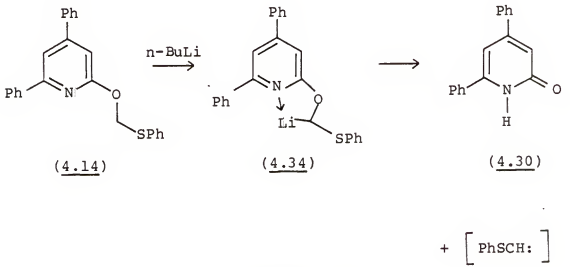
The reaction of 4,6-diphenyl-2-pyridone (4.30) with phenylthiomethyl chloride (4.31) in ethanol in the presence of sodium hydroxide led to recovery of the starting pyridone (4.30). Detection of thiophenol in the reaction mixture suggested that (4.31) was not stable in the presence of hydroxide anion.

The reaction of preformed sodium 2-oxido-4,6-diphenylpyridone (4.32) with benzyl chloride was carried out in order to have a model for the corresponding reaction with phenylthiomethyl chloride (4.31). When (4.32) was treated with benzyl chloride in DMF at room temperature, the expected product (4.33) was obtained in 73% yield (Scheme 4.17). This compound was characterized by singlets at 7.2 and 5.7 p.p.m. in the ^{1}H-n.m.r. spectrum, corresponding to the 3-H and benzylic protons, respectively. More spectroscopic data are given in the experimental section. The structure was supported by elemental (C,H,N) analysis.

Similar treatment of phenylthiomethyl chloride (4.31) yielded the desired product (4.14) in 45% yield (Scheme 4.17). In the ^{1}H-n.m.r. spectrum of (4.14) the 3-H and methylene protons gave singlets at 7.1 and 6.1 p.p.m., respectively. A correct elemental (C,H,N) analysis was obtained for (4.14).

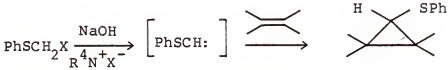
Lithiation reactions of the sulfide (4.14)

Addition of n-butyllithium followed by benzyl chloride to (4.14) in THF at -78 °C, resulted in recovery of the starting material. At room temperature, however, 4,6-diphenyl-2-pyridone (4.30) was isolated in 40% yield (Scheme 4.18). Lowering the reaction temperature to -40 °C resulted in obtention of a (2:3) mixture of the starting material (4.14) and 4,6-diphenyl-2-pyridone (4.30), as shown by the ^{1}H-n.m.r. spectrum of the crude product. No reaction was observed when LDA was used as base.



Scheme 4.18

These results seemed to indicate that at low temperatures (ca. -78 °C) the carbanion (4.34) did not form to any appreciable extent, probably due to insufficeint activation of the methylene protons by the adjacent divalent oxygen and sulfur atoms. At higher temperatures the carbanion (4.34) was probably formed but immediately decomposed to form 4,6-diphenyl-2-pyridine (4.30) and possibly phenylthiomethane carbene (Scheme 4.18). The formation of carbenes of this type has been reported in the literature [75JO2282, 75TL4247]; they are generated from sulfides (4.35) (Scheme 4.19) under basic conditions and can be trapped with olefins or, alternatively, dimerize.



(4.35)

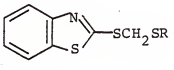
Scheme 4.19

Two modifications were possible in the sulfide (4.14) in order to increase the stability of the corresponding carbanion:

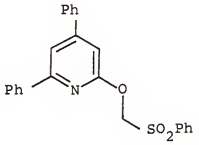
(i) substitution of the oxygen atom by the more activating sulfur; this led to the development of a new system (4.36) and will be dealt with in Section 4.2.4.

(ii) oxidation of the sulfide functionality to the stronger electron-withdrawing sulfone group; this would increase the acidicity of the adjacent methylene protons and disfavor carbene formation.

The reactions of the sulfone (4.37) shall be discussed first.

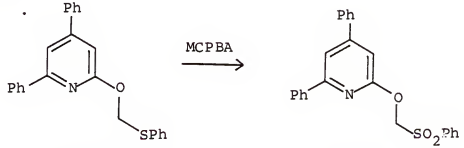


(4.36)



(4.37)

The sulfone (4.37) was prepared in 90% yield by treatment of the sulfide (4.14) with two equivalents of m-chloroperbenzoic acid (MCPBA) in dichloromethane at 0 °C (Scheme 4.20).



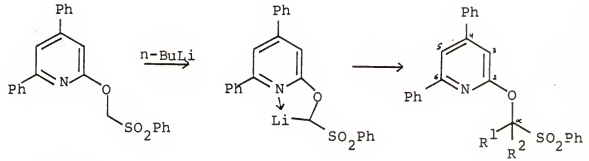
(4.14) (4.37)

Scheme 4.20

The i.r. spectrum of (4.37) showed the asymmetric SO_2 stretching band at 1320 cm^{-1}. In the ^1H-n.m.r. spectrum, two singlets at 7.0 and 5.8 p.p.m. were assigned to the H-3 and methylene protons, respectively. The ^{13}C-n.m.r. spectrum (Table 4.1) supported this structure and will be discussed with the spectra of α-substituted sulfones (vide infra). The sulfone (4.37) gave a correct elemental (C,H,N) analysis.

Lithiation reactions on the sulfone (4.37)

The carbanion derived from the sulfone (4.37) was generated with n-butyllithium in THF at -78 °C and reacted with benzyl chloride, methyl iodide and benzaldehyde to give the corresponding substituted derivatives (4.38) in moderate yields (Scheme 4.21). In the reaction with methyl iodide a mixture of the mono- (4.38c) and dialkylated (4.38d) products was obtained (Scheme 4.21).



(4.37) (4.38)

a R^1=H; R^2=CH_2Ph
b R^1=H; R^2=CHOHPh
c R^1=H; R^2=CH_3
d R^1=R^2=CH_3

Scheme 4.21

A correct elemental (C,H,N) analysis was obtained for the monosubstituted derivatives (4.38a), (4.38b) and (4.38c).

In the i.r. spectrum of sulfones (4.38), the asymmetric SO_2 stretching frequency was in the region 1300-1320 cm^{-1}; the alcohol (4.38b) gave a weak OH band between 3600 and 3450 cm^{-1}. The ^{1}H-n.m.r. spectrum of the benzyl derivative (4.38a) showed 3-H as a singlet at 6.8 p.p.m; the α-proton to the sulfone group resonated with the bulk of aromatic protons whereas the benzylic protons appeared as the AB portion of an ABX system between 3.9 and 3.1 p.p.m. The alcohol (4.38b) displayed in its ^{1}H-n.m.r. spectrum a complicated pattern between 7.0 and 5.4 p.p.m, due to the presence of diastereomers. In the ^{1}H-n.m.r. spectrum of the mixture of (4.38c) and (4.38d) the 3-H and $CHSO_2$ protons overlapped at 7.1 p.p.m.; the methyl group of (4.38c) appeared as a doublet at 1.7 p.p.m. and the methyl groups of (4.38d) resonated as a singlet at 2.1 p.p.m.

The ^{13}C-n.m.r. spectra (Table 4.1) were characteristic and supported the structure of sulfones (4.38). Thus, the quaternary C-2 was downfield with respect to all the other carbons as it resonated in the region 161.4-161.0 p.p.m. [79OMR318]. Likewise, C-6 and C-4 were also deshielded and appeared as singlets at 154.7-152.4 p.p.m. C-5 and C-3 were characteristically shielded [79OMR318], resonating as doublets at 113.5-113.0 and 106.9-106.6 p.p.m., respectively. The aliphatic carbon adjacent to the sulfone group appeared at 88.5-78.1 p.p.m.

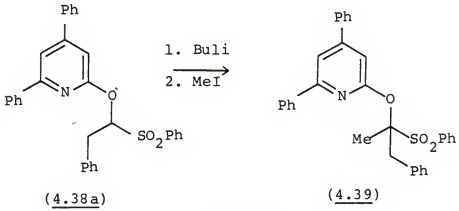
Table 4.1 ^{13}C-N.m.r. spectra of sulfones (4.37) and (4.38)

Compound No.	R^1	R^2	C-2 (s)	C-3 (d)	C-4 (s)	C-5 (d)	C-6 (s)	C-α (d)	R^2
(4.37)	H	H	161.02	106.82	152.93	113.45	154.68	78.16[a]	
(4.38a)	H	CH_2Ph	161.36	106.63	152.49	113.06	154.21	87.23	33.86[b]
(4.38b)	H	CHOHPh	161.08	106.63	152.64	113.35	154.24	88.45	72.07[c] 70.61[c]
(4.38c)	H	CH_3	161.26	106.92	152.73	113.11	154.54	83.96	13.64[d]

Note: All spectra were recorded in $CDCl_3$; values are referred to $CDCl_3$; chemical shifts are given in p.p.m.; s=singlet, d=doublet, t=triplet, q=quartet.
a $\underline{C}H_2$(t). b $\underline{C}H_2$Ph(t). c $\underline{C}$HOH(d). d $\underline{C}H_3$(q)

Lithiation of the sulfone (4.38a)

The preparation of a disubstituted derivative (4.39) from the benzyl substituted sulfone (4.38a) was attempted (Scheme 4.22). Thus, (4.38a) was treated with n-butyllithium in THF at -78 °C, followed by methyl iodide. This led to a mixture of products whose ^{1}H-n.m.r. spectrum showed singlets at 3.8 and 2.0 p.p.m. assigned to the benzylic and methyl protons, respectively, in the expected product (4.39) (Scheme 4.22), along with other signals due to unidentified products. The mixture was not separated.

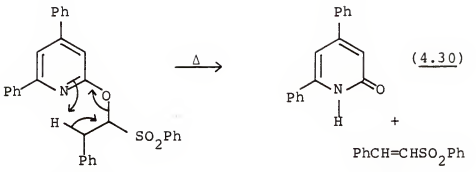


(4.38a) (4.39)

Scheme 4.22

Thermolysis of (4.38a)

The expected products in the thermolysis of (4.38a) are 4,6-diphenyl-2-pyridone (4.30) and the vinyl sulfone (4.40) if an elimination analogous to that reported for 2-alkoxypyridines (see Section 4.1) was to occur (Scheme 4.23).

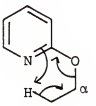


(4.38a) (4.40)

Scheme 4.23

However, (4.38a) was stable when heated neat at temperatures slightly higher than its melting point (162-164 °C) and elimination could only be achieved by heating the melt for 1h at ca. 240 °C. The pyridone (4.30) was then obtained in 40% yield, as shown by i.r. and ^{1}H-n.m.r. spectroscopy (see Experimental section), but the corresponding vinyl sulfone (4.40) could not be isolated due to carbonization.

Mechanistic studies on the thermolysis of 2-alkoxypyridines have shown that the reaction proceeds through the cyclic transition state (4.41) and is the nitrogen analogue of the ester pyrolysis [82J(PII)1175].

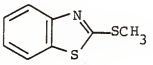


(4.41)

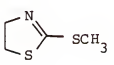
The factors that govern the pyrolysis of esters have been well established [79J(PII)1730]. Thus, increased electron supply to the α-carbon gives an increased elimination rate, since that carbon is partially positively charged in the transition state. The same factors are believed to apply to the thermolysis of 2-alkoxypyridines [82J(PII)1175]. Therefore, a sulfone group on the α-position of (4.38a) should significantly retard the elimination; it is then apparent that the strong electron-withdrawing sulfone group, while being necessary in the lithiation step, is an important factor in the resistance of (4.38a) to undergo elimination.

4.2.2. 2-Alkylthiobenzothiazole Derivatives

It has been reported in the literature that 2-methylthiobenzothiazole (4.42) could not be lithiated with n-butyllithium in THF at -60 °C, the conditions used for the lithiation of 2-methylthiothiazoline (4.43) [74H185]. However, no details as to the reason for the failure were given.



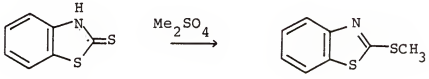
(4.42)



(4.43)

This section deals with the lithiation of (4.42) and other 2-alkylthiobenzothiazoles under LDA/THF conditions. It has been found that n-butyllithium adds to the 2-position of the benzothiazole ring and, as will be discussed later (vide infra), this can be used advantageously for synthetic purposes.

2-Methylthiobenzothiazole (4.42) was prepared in 79% yield from 2-mercaptobenzothiazole (4.44), according to a literature procedure (Scheme 4.24) [49J1503].

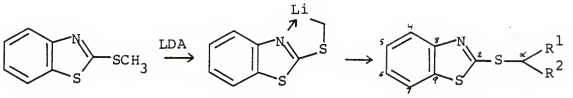


(4.44) (4.42)

Scheme 4.24

Lithiation of 2-methylthiobenzothiazole (4.42)

Treatment of 2-methylthiobenzothiazole (4.42) with LDA in THF at -78 °C yielded a light yellow solution of the lithio-derivative (4.45) which reacted cleanly with a variety of electrophiles to afford the corresponding substituted products (4.46) in good yields (Scheme 4.25). In the reaction with trimethylsilyl chloride the disubstituted product (4.46g) was also isolated in 5% yield. However, carbanion (4.45) failed to give a substitution product with isopropyl iodide, the starting material (4.42) being recovered unchanged.



(4.42) (4.45) (4.46)

	R^1	R^2	(Yield %)
a	CH_3	H	76
b	CH_2CH_3	H	87
c	$n\text{-}C_6H_{13}$	H	72
d	$C(OH)Ph_2$	H	84
e	$C(OH)p\text{-}C_6H_4CH_3$	H	81
f	$SiMe_3$	H	86
g	$SiMe_3$	$SiMe_3$	5
h	$COp\text{-}C_6H_4CH_3$	H	67

Scheme 4.25

The products (4.46) were characterized by their spectral (^{1}H- and ^{13}C-n.m.r.) data and elemental (C,H,N) analysis or high resolution mass spectroscopy. 2-Propylthiobenzothiazole (4.46b) was isolated in a mixture with the starting material (4.42), from which it was separated and identified by g.c./mass spectroscopy (see Experimental).

All the products showed in the ^{1}H-n.m.r. spectrum a characteristic pseudotriplet at ca. 7.9 p.p.m., corresponding to the 4-H and 7-H protons of the benzothiazole ring. Further details are given in the Experimental section. The ^{13}C-n.m.r.

Table 4.2 ^{13}C-N.m.r. spectra of 2-alkylthiobenzothiazoles (4.42) and (4.46)

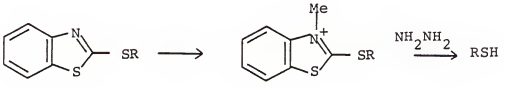
Compound No.	R^1	R^2	C-2 (s)	C-4 (d)	C-5 (d)	C-6 (d)	C-7 (d)	C-8 (s)	C-9 (s)	C-α (t)	R^1
(4.42)	H	H	167.31	120.32	125.39	123.44	120.76	152.73	134.60	15.30[a]	
(4.46c)	n-C_6H_{13}	H	166.87	120.47	125.54	123.64	121.05	153.03	134.85	33.23	b
(4.46d)	Ph_2COH	H	168.43	120.96	126.12	124.51	121.20	152.00	135.38	46.10	77.86[c]
(4.46e)	p-$CH_3C_6H_4CHOH$	H	167.55	120.74	125.93	124.22	121.05	152.30	135.09	42.39	72.95[d] 20.95[e]
(4.46f)	$(CH_3)_3Si$	H	170.38	120.81	125.88	123.78	121.20	153.46	135.24	18.95	-1.75[f]
(4.46h)	p-$CH_3C_6H_4CO$	H	165.16	120.76	125.73	124.03	121.11	152.50	135.15	40.78	192.07[g] 21.42[h]

Note: All spectra were recorded in $CDCl_3$; values are referred to $CDCl_3$; chemical shifts are given in p.p.m.; s=singlet, d=doublet, t=triplet, q=quartet. a $\underline{C}H_3$(q). b 31.33(t), 28.89(t), 28.45(t), 22.31(t), 13.79(q). c $Ph_2\underline{C}OH$(s). d Ar$\underline{C}$HOH(d). e $\underline{C}H_3$Ar(q). f $(\underline{C}H_3)_3Si$(q). g $\underline{C}O$(s). h $\underline{C}H_3$Ar(q).

spectra of products (4.46) (Table 4.2) displayed a very characteristic pattern for the quaternary carbons in the benzothiazole ring [79JOl136]. Thus, C-2 was significantly deshielded resonating in the region 170.4-165.1 p.p.m.; C-8, also characteristically deshielded, appeared at 153.5-152.0 p.p.m., whereas C-9 resonated at 135.4-135.6 p.p.m. These three carbons were easily identified as singlets in the off-resonance spectrum. The remaining aromatic carbons gave signals in the region 145.7-120.3 p.p.m. The C-4 and C-6 carbons in the benzothiazole ring were further downfield than C-7 and C-5, respectively, due to the electron donating effect of the 2-substituent (Table 4.2) [79JOl136]. The α-carbon chemical shifts were widely spread (42.4-15.3 p.p.m.), depending on the group incorporated into the molecule in the lithiation reaction.

Reaction of 2-heptylthiobenzothiazole (4.46c) with n-butyllithium

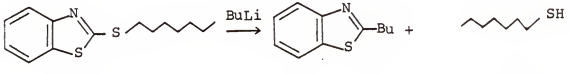
Alkanethiols can be obtained from 2-alkylthiobenzothiazole derivatives in two steps by quaternization of the heterocyclic nitrogen followed by treatment of the resulting benzothiazolium salt (4.47) with hydrazine (Scheme 4.26) [84TL2675].



(4.47)

Scheme 4.26

The same transformation can be accomplished using two equivalents of n-butyllithium at -78 °C. The second equivalent is necessary because some base is consumed in the α-deprotonation (vide infra) of the 2-butylbenzothiazole (4.48) (Scheme 4.27) formed during the reaction. Thus, 2-heptylthiobenzothiazole (4.46c) [prepared in 72% yield from n-hexyl iodide (4.49; R=n-C_6H_{13})] gave a 70% yield of 1-heptanethiol (4.50; R=n-C_6H_{13}) (Scheme 4.27).



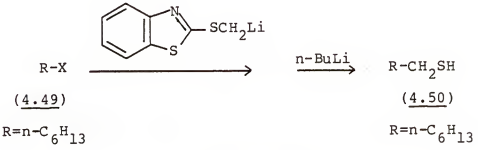
(4.46c) (4.48) (4.50)

Scheme 4.26

1-Heptanethiol was characterized by its boiling point [82MI2866], and ^1H- and ^{13}C-n.m.r. spectra.

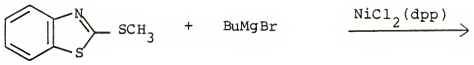
2-Butylbenzothiazole (4.48) was characterized by its ^1H- and ^{13}C-n.m.r. spectra. Thus, its ^1H-n.m.r. spectrum showed the typical pseudotriplet corresponding to the 4-H and 7-H protons on the benzothiazole ring; the α-methylene protons resonated as a triplet at 3.1 p.p.m. The off-resonance ^{13}C-n.m.r. spectrum gave singlets at 171.65, 152.93 and 134.75 p.p.m. for C-2, C-8 and C-9, respectively. The identity of (4.48) was confirmed by mass spectroscopy (see Experimental section).

The overall transformation (4.49) to (4.50) (Scheme 4.28) represents the conversion of an alkyl halide into a thiol with a longer carbon chain by one methylene unit than the original halide. Few examples of the substitution of the halogen atom in alkyl halides by a mercaptomethyl group can be found in the literature [75TL1669, 76S202, 77TL1839]. The present method offers very mild overall conditions for the above mentioned conversion.

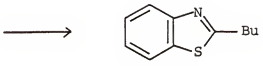


Scheme 4.28

The formation of 2-butylbenzothiazole (4.48) in this reaction can be considered an example of the coupling of an aryl sulfide with an organometallic reagent [for a review see 84T641]. Alkenyl, aryl and allyl sulfides are known to couple with Grignard reagents in the presence of nickel-phosphine complexes. Thus, 2-methylthiobenzothiazole (4.42) reacted with butylmagnesium bromide in boiling ether in the presence of $NiCl_2$(dpp) [dpp = $Ph_2PCH_2CH_2CH_2PPh_2$] to form 2-butylbenzothiazole (4.48) in 93% yield (Scheme 4.29) [79CL1447]. However, the reaction failed to proceed in the absence of the catalyst.



(4.42)



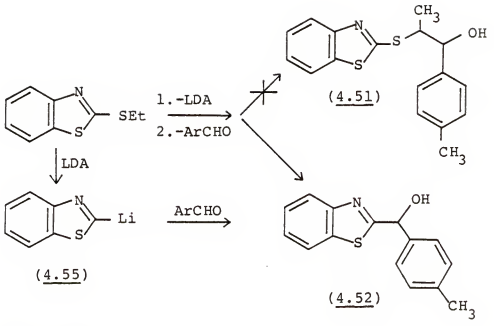
(4.48)

Scheme 4.29

This new reaction with alkyllithiums proceeds at lower temperatures and does not require the presence of a catalyst.

Lithiation of 2-ethylthiobenzothiazole (4.46a)

When (4.46a) was treated with LDA in THF at -78 ^{o}C a familiar yellow solution was obtained. However, the addition of p-tolualdehyde to that solution did not give the expected product (4.51) (Scheme 4.30); instead (4.52) was obtained in 65% yield, as shown by ^{1}H- and ^{13}C-n.m.r., and elemental (C,H,N) analysis.



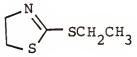
Ar=p-tolyl

Scheme 4.30

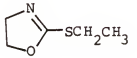
The ^{1}H-n.m.r. spectrum of (4.52) showed a pseudotriplet at 7.9 p.p.m. due to H-4 and H-7 in the benzothiazole ring; the methine and methyl protons gave singlets at 6.1 and 2.3 p.p.m., respectively. In the off-resonance ^{13}C-n.m.r. spectrum of (4.52) three singlets at 175.64, 152.59 and 138.40 p.p.m. were assigned to the quaternary carbons in the benzothiazole ring; the methine carbon gave a doublet at 74.12 p.p.m. Full spectral details are given in the Experimental section.

Two factors contributed to the unexepcted outcome of this reaction:

(i) the low kinetic acidity of the methylene protons in 2-ethylthiobenzothiazole; this has been the reason given [76JO1735] to explain similar failures with 2-ethylthiothiazoline (4.53) [74H185] and 2-ethylthiooxazoline (4.54) [76JO1735];

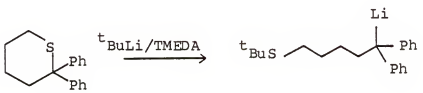


(4.53)



(4.54)

(ii) alkyllithiums are known to cleave carbon-heteroatom bonds to produce a new carbanion. The ease of the reaction increases with the stability of the expelled carbanion [80T2531]; one example of this is shown in Scheme 4.31.

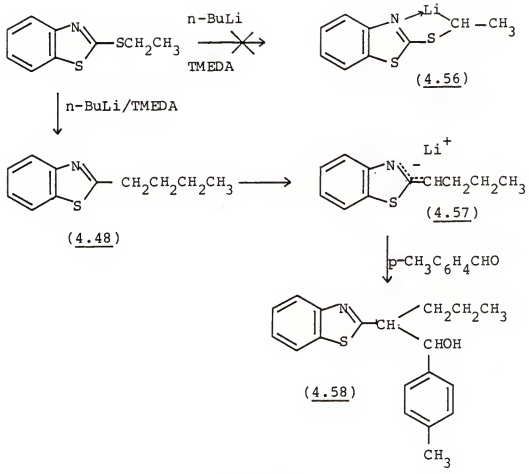


Scheme 4.31

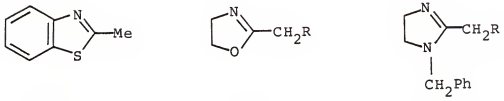
Therefore, in the reaction with 2-ethylthiobenzothiazole, it is reasonable to assume that LDA attacked the exocyclic divalent sulfur to form 2-lithiobenzothiazole (4.55) (Scheme 4.30). This lithio-derivative is stable and adds readily to carbonyl groups [78TL5, 85H295].

The formation of the carbanion (4.56) (Scheme 4.32) was attempted again using n-butyllithium-tetramethylethylenediamine (TMEDA) as base. It was hoped that by means of increasing the basicity of the medium [80T2531] the desired deprotonation would take place. Thus, 2-ethylthiobenzothiazole (4.46a) was treated with n-butyllithium-TMEDA, followed by p-tolualdehyde, but, similarly, under these conditions, the carbanion (4.56) was still not formed. Instead, base attack at the 2-position of the benzothiazole ring took place to form 2-butylbenzothiazole (4.48) (Scheme 4.32). In the presence of n-butyllithium, (4.48) formed a new carbanion (4.57) which reacted with p-tolualdehyde to give the observed product (4.58) in 32% yield, based on n-butyllithium (Scheme 4.32).

The formation of resonance stabilized carbanions similar to (4.57) has been reported for 1-methylbenzothiazole (4.59) [78TL5], 2-alkyloxazolines (4.60) [76JA567] and 2-alkyl-1-benzyl-4,5-dihydroimidazoles (4.61) [84J(PI)2599].



Scheme 4.32



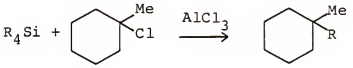
(4.59) (4.60) (4.61)

In the ^{1}H-n.m.r. spectrum of (4.58), the benzothiazole protons gave distinct multiplets at 7.8 and 7.3 p.p.m., separated from the rest of the aromatic protons, that gave a singlet at 7.0 p.p.m. The α- and β-methine protons gave a quartet at 3.9 p.p.m. and a doublet at 4.9 p.p.m., respectively. In the ^{13}C-n.m.r. spectrum the benzothiazole C-2, C-8 and C-9 were found at 173.60, 152.74 and 134.27 p.p.m., respectively. The β-methine carbon bearing the hydroxyl group resonated at 76.61 p.p.m. (doublet) while the α-methine carbon did so at 51.80 p.p.m. (doublet). The identity of (4.58) was confirmed by elemental (C,H,N) analysis.

Attempted desilylation of (4.46f)

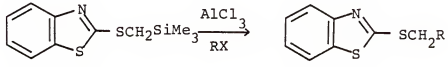
The trimethylsilyl derivative (4.46f) offered a different approach towards the alkylation of 2-alkylthiobenzothiazole derivatives, the alkyl group being different from methyl.

The starting point was a recent review article [84S991] showing the use of tetraalkylsilanes as alkylating agents in Lewis acid-catalyzed reactions with alkyl halides (Scheme 4.33).



Scheme 4.33

This reaction was thought to involve carbocationic intermediates which attacked the C-Si bond [84S991]. Since the reaction must also involve species with a certain carbanionic character, it was thought that in a similar reaction with (4.46f) the alkylthiobenzothiazole portion of this silane would be transferred to the carbocation generated from the alkyl halide to afford (4.62) (Scheme 4.34).

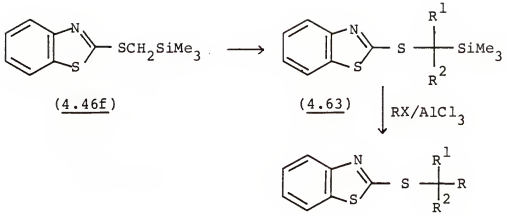


(4.46f) (4.62)

Scheme 4.34

Furthermore, carbanions simultaneously stabilized by sulfur and silicon have been studied by Ager and found to react readily with electrophiles [83J(PI)1131]. The complete sequence would then involve consecutive carbanion mediated alkylations of (4.46f) to form (4.63), followed by replacement of the trimethylsilyl moiety by an alkyl group under Lewis acid conditions (Scheme 4.35).

Thus, the silane (4.46f) was mixed in equimolar amounts with t-butyl chloride and aluminum chloride in dry dichloromethane at -78 °C; the mixture was then allowed to warm to room temperature, following the conditions reported for tetramethylsilane [84S991]. However, this resulted in recovery



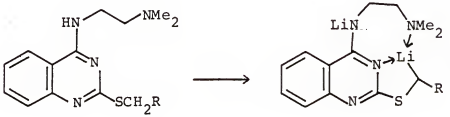
Scheme 4.35

of the starting silane (4.46f). The use of two or three equivalents of aluminum chloride gave the same result. When the reactants were mixed at room temperature, the immediate evolution of hydrochloric acid that took place indicated that the halide was undergoing elimination. This was probably also the result at low temperatures, although the rate of elimination was then slower.

4.2.3 2-Alkylthioquinazoline Derivatives

The failures obtained with the benzothiazole system with respect to the introduction of at least two groups different from hydrogen on the S-Me carbon led to the device of a new system (4.64) (Scheme 4.36). The carbanion (4.65) derived from (4.64) was expected to take advantage of the same stabilizing factors that operated in 2-methylthiobenzothiazole and

the additional stabilization provided by the coordination with the dimethylamino nitrogen. Furthermore, the presence of the acidic NH in (4.64) would result in the deactivation of the heterocyclic ring of (4.65) towards nucleophilic addition by the base. This would make it possible to use stronger bases than LDA, such as n-butyllithium or t-butyllithium.

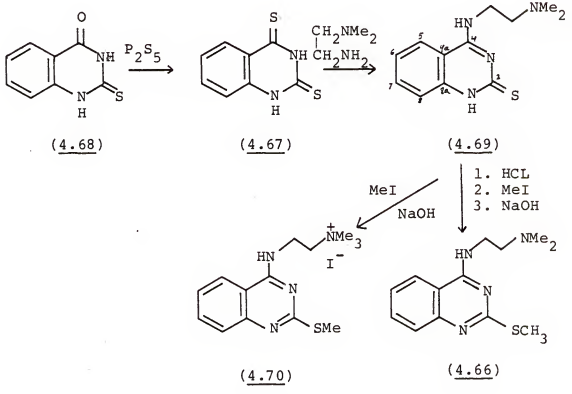


(4.64) (4.65)

Scheme 4.36

The idea was tested on the simple 2-methylthioquinazoline derivative (4.66). The synthesis of this compound was accomplished by the route shown in Scheme 4.37. This took advantage of the selective replacement by amines of the 4-mercapto group in 2,4-dimercaptoquinazoline (4.67) [62JO957].

A literature procedure [47JA2138] was followed to prepare (4.67) from the commercially available 2-mercapto-4-quinazolinone (4.68) and phosphorus pentasulfide (Scheme 4.37).



(4.68) (4.67) (4.69)

(4.70) (4.66)

Scheme 4.37

The reaction of (4.67) and N,N-dimethylethylenediamine in refluxing n-butanol afforded a 93% yield of the 4-alkylaminoquinazoline-2-thione (4.69) which was characterized by its spectral (^{1}H- and ^{13}C-n.m.r.) and elemental (C,H,N) analyses. Thus, in its ^{1}H-n.m.r. spectrum, the ethylene protons gave triplets at 3.9 and 2.7 p.p.m. and the dimethylamino protons appeared as a singlet at 2.3 p.p.m. The ^{13}C-n.m.r. spectrum was revealing in that one of the

thiocarbonyl groups [which in 2,4-dimercaptoquinazoline (4.67) resonated at 187.61 and 170.43 p.p.m.] had been substituted by a new quaternary carbon at 156.15 p.p.m., corresponding to C-4 in (4.69). The other thiocarbonyl carbon appeared at 180.32 p.p.m. C-8a and C-4a were identified by singlets in the off-resonance spectrum at 140.59 and 109.70 p.p.m., respectively; these values were in agreement with literature data for related compounds [76OMR357, 79OMR212]. The evidence for substitution at the 4- rather than at the 2- position was given by the 12.93 p.p.m. upfield shift observed for C-4a when (4.67) was converted into (4.69); this was due to the stronger ortho effect of the amino group when compared to the mercapto group [81MI265]. Thus, C-4a resonated at 109.70 p.p.m. in (4.69) whereas the chemical shift for the same carbon in (4.67) was 122.63 p.p.m. C-8a had comparable values in (4.67) and (4.69).

The reaction of (4.69) (Scheme 4.37) with methyl iodide in the presence of aqueous sodium hydroxide at room temperature resulted in methylation at both the divalent sulfur, as desired, and the dimethylamino nitrogen,to afford the salt (4.70) in 60% yield, based on methyl iodide. This compound was characterized by its elemental (C,H,N) analysis, and ^{1}H- and ^{13}C-n.m.r. spectra (see Experimental section).

The desired 2-methylthioquinazoline derivative (4.66) was obtained (Scheme 4.37) upon treatment of a solution of (4.69) in aqueous hydrochloric acid with methyl iodide at room

temperature and subsequent liberation of the free amine with aqueous sodium hydroxide.

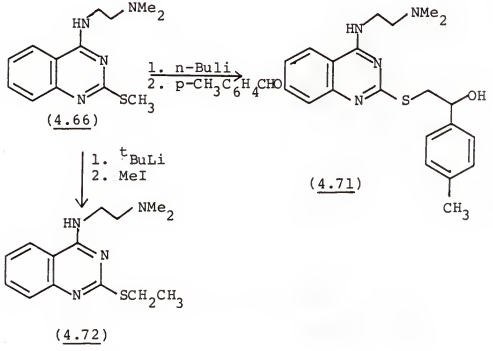
The ^{13}C-n.m.r. chemical shifts of the quaternary carbons in (4.66) were characteristic. C-2, C-4 and C-8a gave singlets in the off-resonance spectrum at 167.33, 158.14 and 150.30 p.p.m., respectively, deshielded by direct heteroatom substitution at these positions. C-4a, however, resonated at 112.39 p.p.m., considerably shielded by the ortho effect of the 4-amino substituent. The thiomethyl carbon gave a quartet at 13.59 p.p.m. The ^{1}H-n.m.r. data (see Experimental section) and elemental (C,H,N) analysis supported the structure.

Lithiation of the 2-methylthioquinazoline (4.66)

An exothermic reaction was observed when (4.66) was treated with two equivalents of n-butyllithium in THF at -78 °C but, after addition of p-tolualdehyde at the same temperature, (4.66) was recovered unchanged, as judged by ^{1}H-n.m.r. inspection of the crude product.

Some product formation was observed when the reaction was carried out at 0 °C after addition of n-butyllithium at -78 °C. Chromatography of the crude reaction mixture afforded two main fractions in a ca. 50:50 ratio by weight. One of the fractions contained the starting material (4.66) and what appeared to be the expected product (4.71) (Scheme 4.38). This conclusion was reached after inspection of the ^{1}H-n.m.r. spectrum of this fraction, where a triplet at 5.2 p.p.m. was assigned to the proton on the methine carbon bearing the hydroxyl group of (4.71).

The remaining peaks and integration were consistent with a ca. 4:3 mixture of (4.71) and (4.66). The other major fraction consisted of a mixture of products which could not be characterized.



Scheme 4.38

As an alternative, the deprotonation step was carried out with t-butyllithium in THF at -78 °C. Treatment of the resulting red solution with methyl iodide resulted in the formation of the 2-ethylthioquinazoline derivative (4.72) (Scheme 4.38), as evidenced by the presence of a quartet and a triplet at 3.2 and 1.4 p.p.m., respectively, in the

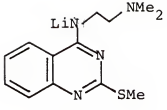
^{1}H-n.m.r. spectrum. However, this also showed that ca. 40% of the starting material (4.66) had been recovered. The presence of other products was observed by t.l.c..

No incorporation of deuterium was observed when (4.66) was treated with two equivalents of LDA at 0 °C and the reaction mixture was quenched with D_2O.

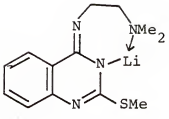
These results indicated that the thiomethyl protons of (4.66) were not acidic enough to be removed by n-butyllithium or LDA at low temperatures (-78 °C). When higher temperatures (ca. 0 °C) or the stronger base t-butyllithium were used, the formation of the corresponding carbanion was possible but other unknown reactions also took place.

The lack of reactivity of the thiomethyl protons towards the base can be understood in terms of the deactivation brought to the system by the deprotonation of the acidic NH on the 4-position of the quinazoline ring. The resulting anion can adopt the two structures (4.73) and (4.74).

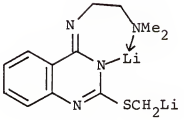
The contribution from (4.74) would prevent the lithium atom related to the carbanionic center in (4.75) from being chelated by the nitrogen atoms. Besides, the presence of a negative charge on the quinazoline ring would make the dipole stabilization of the carbanion much more difficult.



(4.73)

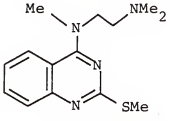


(4.74)



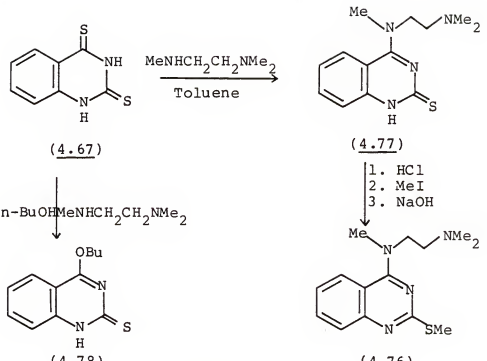
(4.75)

Those considerations suggested that the quinazoline derivative (4.76), where the acidic NH had been substituted by a methyl group, could give the desired results.



(4.76)

The preparation of (4.76) was not possible by treatment of the quinazoline-2-thione (4.66) with base and methyl iodide because of the competing methylation on the dimethylamino group (vide supra). Therefore, (4.76) had to be prepared from the corresponding quinazoline-2-thione (4.77) (Scheme 4.39)



(4.67) (4.77) (4.78) (4.76)

Scheme 4.39

The reaction of 2,4-dimercaptoquinazoline (4.67) with N,N,N'-trimethylethylenediamine in refluxing n-butanol led to a mixture of the expected product (4.77) and 4-butoxyquinazoline-2-thione (4.78) (Scheme 4.39). From this mixture, (4.78) was isolated in 35% yield. The thione (4.78) was identified by the absence of the ethylenediamino group in the ^{1}H-n.m.r. spectrum and presence of a triplet at 4.7 p.p.m. and multiplets in the region 2.0-0.8 p.p.m. with the appropriate integration.

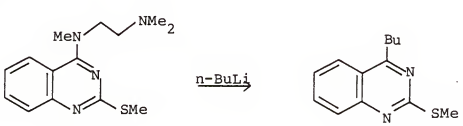
The desired thione (4.77) was prepared in 62% yield by refluxing (4.67) with excess (ca. three equivalents) of N,N,N'-trimethylethylenediamine in toluene (Scheme 4.39).

It was characterized by its elemental (C,H,N) analysis and by the analogy of its spectral (^{1}H- and ^{13}C-n.m.r.) data (see Experimental section) with those of the thione (4.69) previously prepared.

The same procedure used to make the thiomethyl derivative (4.66) (Scheme 4.37) was employed to prepare (4.76) in 80% yield from (4.77) (Scheme 4.39). This was characterized by its spectral (^{1}H- and ^{13}C-n.m.r.) data (see Experimental section) and elemental (C,H,N) analysis.

Lithiation of the 2-methylthioquinazoline (4.76)

The treatment of (4.76) with LDA at temperatures ranging from -78 °C to 25 °C, followed by addition of p-tolualdehyde, always resulted in recovery of starting materials. When LDA was replaced by n-butyllithium, the ^{1}H-n.m.r. spectrum of the crude reaction mixture showed, in addition to the presence of unreacted starting material (4.76), that replacement of the 4-substituent by a butyl group had probably taken place to form (4.79) (Scheme 4.40). This was suggested by the presence of triplets at 3.2 and 0.9 p.p.m., and a multiplet at 2.0-1.1 p.p.m., all assigned to the butyl group, and a singlet at 2.7 p.p.m. that was assigned to the S-Me protons of (4.79).



(4.76) (4.79)

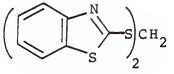
Scheme 4.40

These results clearly indicated that the quinazoline system was not suitable for these carbanion mediated transformations and the investigation was thus abandonned.

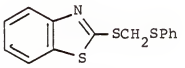
4.2.4 Benzothiazole-Dithioacetal Derivatives

As discussed earlier (see Section 4.1) a methylene group activated by two divalent sulfur atoms, where at least one of the sulfurs was connected to a heterocyclic system, offered interesting synthetic possibilities.

In this respect, the study of the carbanionic reactions of the dithioacetals (4.80) and (4.81) was undertaken.

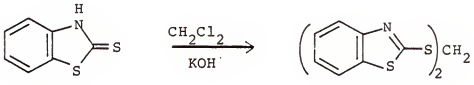


(4.80)



(4.81)

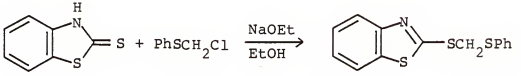
The symmetrical compound (4.80), that was a known compound, was prepared according to the literature procedure (Scheme 4.41) [55J933].



(4.44) (4.80)

Scheme 4.41

The unsymmetrical compound (4.81) was prepared in 90% yield by stirring at room temperature a solution of 2-mercaptobenzothiazole (4.44) in sodium ethoxide-ethanol with phenylthiomethyl chloride (4.31) (Scheme 4.42).



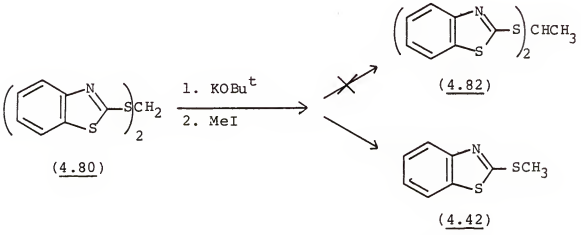
(4.44) (4.31) (4.81)

Scheme 4.42

Compound (4.81) was obtained as an oil that decomposed partially on distillation giving off thiphenol. However, the crude product was sufficiently pure by t.l.c. (silica gel; dichloromethane) and spectroscopic analysis to be used without further purification. The ^{1}H-n.m.r. spectrum of (4.81) (Table 4.3) showed a characteristic pseudotriplet at ca. 7.9 p.p.m., assigned to the H-4 and H-7 protons in the benzothiazole ring; the methylene protons gave a singlet at 4.8 p.p.m. In the off resonance ^{13}C-n.m.r. spectrum (Table 4.4), the typical pattern for the quaternary carbons in the benzothiazole ring could be observed (see Section 4.2.2), while the methylene carbon gave a triplet at 38.91 p.p.m. The high resolution mass spectroscopy data supported this structure.

Metallation of the dithioacetals (4.80) and (4.81)

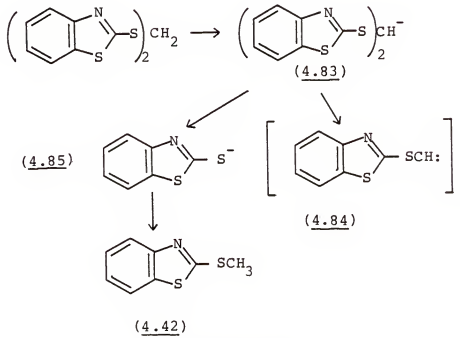
The symmetrical derivative (4.80) was treated with potassium t-butoxide in DMSO at room temperature, and methyl iodide was added to the resulting red solution. The product obtained after the work-up procedure was not the desired methylated derivative (4.82) but 2-methylthiobenzothiazole (4.42) (Scheme 4.43). This was characterized by comparison of its ^{1}H- and ^{13}C-n.m.r. spectra with those of the authentic material (see Section 4.2.2).



Scheme 4.43

The formation of 2-methylthiobenzothiazole (4.42) suggests that the carbanion (4.83) decomposed at room temperature to form the thiomethane carbene (4.84) and the anion (4.85) (Scheme 4.44) in a reaction similar to that undergone by the alkoxypyridine (4.14) (Scheme 4.18; Section 4.2.1). The anion (4.85) then reacted with methyl iodide

to give the observed product (4.42). However, the carbene (4.84) is unknown and no direct evidence for its formation was obtained.

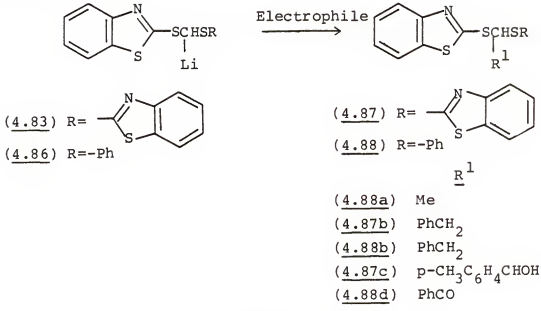


Scheme 4.44

Stable carbanions derived from (4.80) and (4.81) were generated with either n-butyllithium or LDA in THF at -78 °C as intense red solutions. Quenching these solutions with D_2O resulted in incorporation of deuterium on the methylene group as shown by the decrease in the integration of the methylene protons with respect to the aromatic ones. The extent of deuteration was 98 and 93% for (4.80) and (4.81), respectively.

It is noteworthy that the treatment of the benzothiazole derivatives (4.80) and (4.81) with n-butyllithium did not result in attack at the 2-position of the benzothiazole ring, as was observed with 2-alkylthiobenzothiazoles (see Section 4.2.2). Evidently, the presence of a second activating group in (4.80) and (4.81) increases the kinetic acidity of the protons at the adjacent methylene group enough to favor deprotonation over nucleophilic attack.

The carbanions (4.83) and (4.86) generated from (4.80) and (4.81), respectively, could be trapped with reactive electrophiles such as methyl iodide, benzyl bromide, p-tolualdehyde and benzoyl chloride to give the corresponding substituted products (4.87) and (4.88)(Scheme 4.45) in good yields. However, the starting materials were recovered when less reactive electrophiles such as methyl benzoate and n-butyl bromide were used.



Scheme 4.45

Table 4.3 ^{1}H-N.m.r. spectra of dithioacetals (4.80), (4.81), (4.87) and (4.88)

Compound No.	R	R^1	4,7-H δ	(pt) H	Other aromatic protons (m) δ	H	α-H δ	H	M	R^1 δ	H	M
(4.80)	benzth[a]	H	8.0	4	7.7-7.2	4	5.4	2	s			
(4.81)	Ph	H	7.9	2	7.7-7.2	7	4.8	2	s			
(4.87b)	benzth[a]	$PhCh_2$	7.9	4	7.7-7.2	11	6.2	1	t[b]	3.7	2	d[b]
(4.87c)	benzth[a]	$p\text{-}CH_3C_6H_4CHOH$	c		8.1-7.0	12	6.7-6.2[d]		m	5.7[e]	1	br
										2.2[f]	3	s
(4.88a)	Ph	CH_3	7.95	2	7.8-7.2	7	5.4	1	q[g]	1.8	3	d[g]
(4.88b)	Ph	$PhCH_2$	7.85	2	7.7-7.2	12	5.5	1	dd[h]	3.5	2	dd,dd[i]
(4.88d)	Ph	PhCO	c		8.3-7.1	14	7.0	1	s	c		

Note: All spectra recorded in $CDCl_3$ with TMS as internal reference; δ=chemical shift (p.p.m.), J=coupling (Hz), H=number of protons, M=multiplicity, s=singlet, d=doublet, t=triplet, q=quartet, pt=pseudo triplet, dd=double doublet, m=multiplet, br=broad. a Benzothiazol-2-yl. b J 7. c With rest of aromatic protons. d Obscured by OH in the same region. e CHOH. f CH_3Ar. g J 7. h J 6,8. i J 6,8,14.

Table 4.4 ^{13}C-N.m.r. spectra of dithioacetals (4.80), (4.81), (4.87) and (4.88)

Compound No.	R	R^1	C-2 (s)	C-8 (s)	C-9 (s)	Rest of aromatic carbons	C-α (d)	R^1
(4.80)	benzth[a]	H	164.57	152.64	135.38	125.96-120.87	36.28[b]	
(4.81)	Ph	H	164.85	152.74	c	133.96-120.79	38.95[b]	
(4.87b)	benzth[a]	$PhCH_2$	163.80	152.93	c	136.84-120.91	56.04	42.10[d]
(4.87c)	benzth[a]	$p\text{-}CH_3C_6H_4CHOH$	164.72	152.15	135.24	137.43-120.66	63.06	75.87[e]
			163.99					20.90[f]
(4.88a)	Ph	CH_3	164.97	152.93	135.24	132.99-120.86	51.41	22.90[g]
(4.88b)	Ph	$PhCH_2$	165.06	153.03	135.14	137.43-120.96	57.74	42.25[h]
(4.88d)	Ph	PhCO	163.58	152.35	c	135.09-120.81	59.50	190.02[i]

Note: All spectra were recorded in $CDCl_3$; values are referred to $CDCl_3$; chemical shifts are given in p.p.m.; s=singlet, d=doublet, t=triplet, q=quartet. a Benzothiazol-2-yl. b $\underline{C}H_3$(t). c It could not be unambiguously assigned. d $Ph\underline{C}H_2$(t). e $\underline{C}HOH$(d). f $\underline{C}H_3Ar$(q). g $\underline{C}H_3$(q). h $Ph\underline{C}H_2$(t). i $\underline{C}O$(s).

All the products (4.87) and (4.88) were characterized by their ^{1}H- and ^{13}C-n.m.r. spectra. (4.87b) and (4.88b) gave a correct elemental (C,H,N) analysis, while a correct accurate molecular weight was obtained for (4.88a). (4.88d) was obtained as an oil that decomposed on distillation and (4.87c) was a gummy solid that could not be crystallized.

All the substituted derivatives (4.87) and (4.88) showed a pseudotriplet in the ^{1}H-n.m.r. spectrum (Table 4.3) at 7.8-7.9 p.p.m. due to the H-4 and H-7 benzothiazole protons. The chemical shift for the methine proton ranged from 5.4 to 7.0 p.p.m., depending on the group introduced as the electrophile. In the ^{13}C-n.m.r. spectra (Table 4.4), the quaternary carbons C-2 and C-8 of the benzothiazole ring were identified as singlets in the off-resonance spectrum at 165.06-163.58 and 153.03-152.15 p.p.m., respectively. The methine carbon gave a characteristic doublet in the region 63.06-51.41 p.p.m.

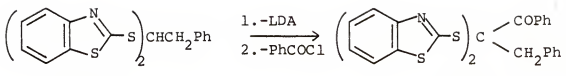
Lithiation of the benzyl derivatives (4.87b) and (4.88b)

This was first studied by treating (4.87b) and (4.88b) with n-butyllithium in THF at -78 ^{o}C, followed by quenching with D_2O and analysis of the crude reaction mixture by ^{1}H-n.m.r. spectroscopy and t.l.c. This revealed that deuterium had been incorporated to only a small extent (ca. 10-15%) and that unwanted side reactions were taking place. Thus the ^{1}H-n.m.r. spectrum showed aliphatic protons, presumably due to a butyl group, and the presence of several products was observed by t.l.c. (silica gel, benzene).

A possible explanation for this is that proton abstraction was slow (due to steric hindrance) when compared to the nucleophilic attack at the benzothiazole 2- position.

This seemed to be supported by the fact that treatment of the symmetrical derivative (4.87b) with LDA (instead of n-butyllithium) and D_2O led to 83% deuteration as shown by the disappearance of the methine proton in the ^1H-n.m.r. spectrum and collapse of the CH_2Ph doublet into a singlet.

However, the reaction of (4.87b) with LDA and benzyl bromide resulted only in recovery of the starting material (4.87b). The corresponding reaction with benzoyl chloride (Scheme 4.46) gave a mixture of products, as shown by t.l.c. (silica gel, benzene), one of which was the unreacted starting material (4.87b). Upon chromarographic separation of the mixture, a fraction was obtained whose ^{13}C-n.m.r. spectrum contained the peaks expected for the benzoylated product (4.89). Thus, a carbonyl carbon appeared at 193.42 p.p.m. and peaks at 160.07, 152.88 and 137.61 p.p.m. could be assigned to the quaternary carbons of the benzothiazole rings. The aliphatic region showed a quaternary carbon at 77.94 p.p.m. and a methylene carbon at 42.54 p.p.m. However, the presence of additional peaks, particularly in the aromatic region, revealed the presence of small amounts of other products as well.



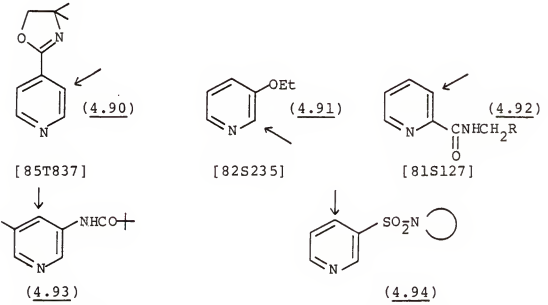
(4.87b) (4.89)

Scheme 4.46

4.2.5 Metallation of Pyridines

Until recent years, the direct metallation of pyridines on a ring CH was limited to a few examples because organolithium reagents normally add across the C=N bond [74MI112].

Now, however, the introduction of certain substitutents on the pyridine nucleus allows regioselective metallations (ortho-metallations) in several cases. Some examples are shown by (4.90)-(4.94).



(4.90) [85T837]

(4.91) [82S235]

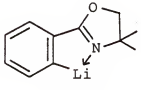
(4.92) [81S127]

(4.93) [81JO3564]

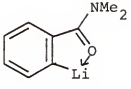
(4.94) [83S822]

The general mechanism of ortho-directed lithiations has been discussed in Chapter I of this dissertation.

Comparative studies [79JO4463, 79JO4464] of the ability of different groups to direct ortho-lithiation have shown that ring strain in the lithiated product reduces the directing ability of groups which are part of a cyclic system [85T837]. Thus, it was found that (4.95) was inferior to (4.96)

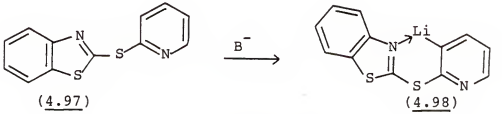


(4.95)



(4.96)

As a further application of the ability of the benzothiazol-2-ylthio- moiety in promoting the formation of stable carbanionic species (see Sections 4.2.2 and 4.2.4), it was interesting to test its ortho-directing effect in the lithiation of the pyridine (4.97) (Scheme 4.47). The presence of the sulfur linkage between the heterocyclic moieties would render the carbanion (4.98) free of the ring strain that hindered the effect of the oxazoline group.

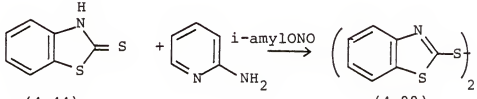


(4.97) (4.98)

Scheme 4.47

Preparation of the pyridine (4.97)

Following a procedure described in the literature for aliphatic amines [84TL2675], 2-mercaptobenzothiazole (4.44) was reacted with 2-aminopyridine in the presence of isoamyl nitrate. However, this resulted in the exclusive formation of the disulfide (4.99) (Scheme 4.48) instead of the desired product (4.97). The disulfide (4.99) was characterized by comparison of it melting point and i.r. spectrum with the corresponding data obtained from the authentic material prepared by a literature method [23JA2396].

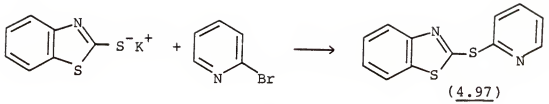


(4.44) (4.99)

Scheme 4.48

The formation of small amounts of the disulfide (4.99) had been reported as a side reaction in the preparation of sulfides from 2-mercaptobenzothiazole and aliphatic amines in the presence of alkyl nitrates [84TL2675].

The pyridine (4.97) could, however, be prepared by reacting the potassium salt of 2-mercaptobenzothiazole with 2-bromopyridine in refluxing DMF (Scheme 4.49).



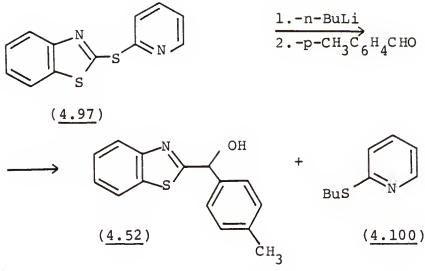
(4.97)

Scheme 4.49

2-(Benzothiazol-2-ylthio)pyridine (4.97) was characterized by a doublet at 8.7 p.p.m. in the ^{1}H-n.m.r. spectrum, corresponding to the 6-H of the pyridine ring. The remaining protons gave a multiplet between 8.2 and 7.1 p.p.m. In the ^{13}C-n.m.r. spectrum the benzothiazole C-2', C-8' and C-9' carbons were found at 162.14, 152.30 and 135.83 p.p.m. respectively. The pyridine carbons were assigned by reference to the chemical shifts of 2-methylthiopyridine [79OMR379]. Thus, the quaternary C-2 resonated at 154.20 p.p.m., H-6 and H-4 gave doublets, in the off-resonance spectrum, at 149.52 and 137.04 p.p.m., respectively. The pyridine C-3 and C-5 overlapped with the remaining benzothiazole carbons in the region 125.83-120.66 p.p.m.

Lithiation of the pyridine (4.97)

Lithiation reactions that occur via a "coordination only" mechanism [79OR1] are found to give greater regioselectivity when n-butyllithium rather than LDA is used as base [85J(PI)173]. However, the reaction of the pyridine (4.97) with n-butyllithium and p-tolualdehyde in THF at -78 °C led to the formation of the alcohol (4.52) in 62% yield and 2-butylthiopyridine (4.100) in 59% yield (Scheme 4.50).

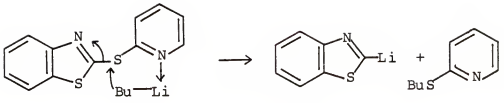


(4.97) (4.52) (4.100)

Scheme 4.50

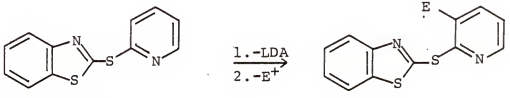
The alcohol (4.52) was characterized by comparison of its physical properties (melting point, ^{1}H-n.m.r.) with those of the authentic material previously characterized (see Section 4.2.2). 2-Butylthiopyridine was characterized by its ^{1}H-n.m.r. spectrum and high resolution mass spectroscopy (see Experimental section).

This reaction is yet another example (see Section 4.2.2) of the known tendency of organolithium reagents to break heteroatom-carbon bonds, and in doing so, expel a stable carbanion (Scheme 4.51) [80T2531]. However, it is interesting that this reaction took place in preference to attack at the benzothiazole 2-position which (as seen in Section 4.2.2) was the exclusive reaction with 2-heptylthiobenzothiazole. The reason for this difference is probably the strong coordinateing effect of the pyridine nitrogen, that directs the attack to the exocyclic sulfur atom (Scheme 4.51).



Scheme 4.51

Treatment of the pyridine (4.97) with LDA in THF at -78 °C resulted in the formation of a deep red solution to which p-tolualdehyde or trimethylsilyl chloride were added. This afforded the corresponding 2,3-disubstituted pyridines (4.101) and (4.102) (Scheme 4.52) in 31 and 27% yield, respectively. These compounds were characterized by their spectral (^{1}H- and ^{13}C-n.m.r.) properties and elemental (C,H,N) analyses.



(4.97)

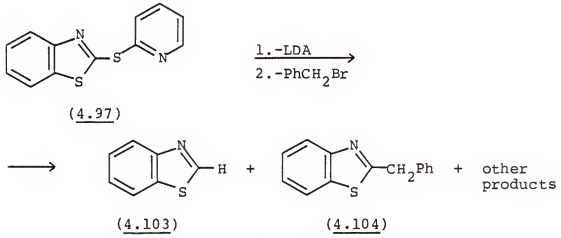
(4.101) E=p-$CH_3C_6H_4CHOH$

(4.102) E=$SiMe_3$

Scheme 4.52

The analogous reaction with p-methylbenzoate gave a complex mixture which was not separated. Benzyl bormide also gave a mixture from which benzothiazole (4.103) and 2-benzylbenzothiazole (4.104) (Scheme 4.53) were separated

by chromatography. (4.104) was characterized by its ^{1}H- and ^{13}C-n.m.r. spectra and high resolution mass spectroscopy (see Experimental section). Other products could not be separated from the reaction mixture.



(4.97) (4.103) (4.104)

Scheme 4.53

Again these results can be rationalized by the base attacking the exocyclic sulfur atom of (4.97) to release 2-lithiobenzothiazole which reacted with a proton or benzyl bromide to give the observed products.

Spectroscopic properties of 2,3-disubstituted pyridines

The disubstituted pyridine (4.101) gave two singlets in the ^{1}H-n.m.r. spectrum at 2.3 and 6.2 p.p.m. (in the presence of D_2O), corresponding to the methyl and methine protons, respectively, whereas the pyridine 6-H gave a doublet at 8.8 p.p.m. The unambiguous differentiation between the 2,3- and 2,4-disubstitution patterns in the pyridine ring was not possible from the 60MHz ^{1}H- and ^{13}C-n.m.r. data (see Experimental).

However, the 300 MHz ^{1}H-n.m.r. spectrum gave the required information. Thus, the 2,3-disubstitution pattern was clearly stated by the double doublet observed for the pyridine 6-H; the coupling constants [J(5-6) = 4.7 Hz and J(4-6) = 1.7 Hz] were in agreement with typical values for pyridines [81MI236]. Spin decoupling experiments allowed the assignments of the pyridine H-4 and H-5 at 8.0 and 7.5-7.45 p.p.m., respectively. As expected [81MI236], the coupling constant J(4-5) was larger (*ca*. 7.7 Hz) than J(5-6). The complete assignments are shown in Figure 4.1.

The trimethylsilyl derivative (4.102) showed, as main features in the ^{1}H-n.m.r. spectrum, a doublet at 8.8 p.p.m. and a singlet at 0.4 p.p.m., due to the pyridine 6-H and trimethylsilyl protons, respectively. The ^{13}C-n.m.r. data confirmed the structure and the 2,3-disubstitution pattern. This was evident from the presence of the pyridine C-6 and C-4 as doublets (off-resonance) at 149.57 and 143.48 p.p.m., respectively [79OMR379]. The chemical shift difference of 6.4 p.p.m. between the C-4 carbons in (4.102) and the parent compound (4.97) was within the expected range due to the presence of a trimethylsilyl group on the adjacent carbon in (4.102) [79OMR499]. Likewise, C-2 was deshielded by 4.1 p.p.m. with respect to the same carbon in (4.97). Correspondingly, C-3, that in the parent compound (4.97) was presumed to be between 125.83 and 120.66 p.p.m., experienced a large downfield shift in (4.102) due to the presence of the trimethylsilyl group at that position, resonating at 137.14 p.p.m.

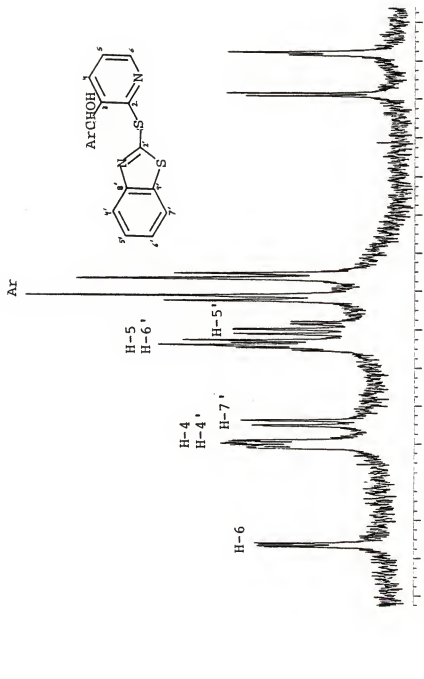
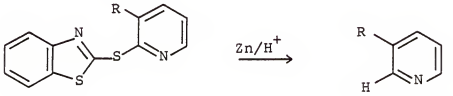


Figure 4.1. 300 MHz ^{1}H-n.m.r. spectrum of the aromatic region of 2-(benzothiazol-2-ylthio)-3-[hydroxyl(4-methylphenyl)methyl]pyridine (4.101)

Outlook

The use of an ortho-directing group linked to the pyridine nucleus by a divalent sulfur has the potential for further transformations of the disubstituted products.

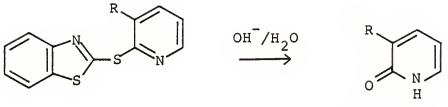
Thus, desulfurization with Zn under acidic conditions [60CB1590] would lead to 3-substituted pyridines (4.105) (Scheme 4.54), which are difficult to make by direct electrophilic substitution on pyridine [84MI186].



(4.105)

Scheme 4.54

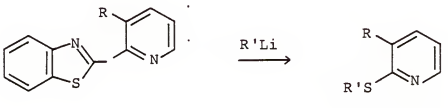
The formation of 2-pyridone upon base treatment of 2-ethylthiopyridine has been reported [69KGS677]. If 3-substituted compounds derived from (4.97) were used, 3-substituted 2-pyridones (4.106) could be obtained (Scheme 4.55).



(4.106)

Scheme 4.55

Lastly, the reaction of (4.97) with n-butyllithium to afford 2-butylthiopyridine (vide supra) could give an entry into different 3-substituted 2-alkylthiopyridines (4.107), depending on the organolithium used (Scheme 4.56).



(4.107)

Scheme 4.56

4.3 Conclusions

The carbanion derived from 2-(phenylthiomethoxy)-4,6-diphenylpyridine (4.14) was not stable enough to be trapped with electrophiles. Instead, it decomposed to 4,6-diphenyl-2-pyridone (4.30) and presumably phenylthiomethane carbene.

The oxidation of the sulfide functionality of (4.14) to form the sulfone (4.37) resulted in enhanced stability of the corresponding carbanion, which could be trapped by electrophiles. However, the thermolysis of the product 4,6-diphenyl-2-(phenylsulphonylmethoxy)pyridine (4.38a) , derived from (4.37), required very high temperatures to proceed and was not of synthetic utility.

2-Methylthiobenzothiazole (4.42) was lithiated at the methyl position with LDA/THF and the lithio-derivative was trapped with a variety of electrophiles. Under the same conditions, 2-ethylthiobenzothiazole (4.46a) did not form a carbanion at the methylene position. Instead, 2-lithiobenzothiazole was generated, probably by base-promoted heterolysis of a C-S bond.

The reaction of 2-alkylthiobenzothiazoles with n-butyllithium afforded 2-butylbenzothiazole and the alkanethiol. When combined with the alkylation of 2-methylthiobenzothiazole, the reaction is a method for the mercaptomethylation of alkyl halides under very mild non-reductive conditions.

The reaction also showed that the coupling between benzothiazol-2-yl sulfides and alkyllithiums occurs readily at -78 ^{o}C in the absence of transition metal catalysts.

The replacement of a hydrogen atom in 2-methylthiobenzothiazole (4.42) by a benzothiazol-2-ylsulphenyl (4.80) or phenylsulphenyl (4.81) moiety resulted in increased reactivity of the methylene group towards deprotonation. The corresponding carbanions could be trapped by electrophiles. However, the possible use of these systems as acyl anion equivalents was severely limited by the failure of the carbanions to react with unactivated alkyl halides and the problems encountered in the introduction of a second group at the active position.

The generation of synthetically useful carbanions derived from 4-(N,N-dimethylethylenediamino)-2-(methylthio)quinazoline (4.66) and 4-(N,N,N'-trimethylethylenediamino-2-(methylthio)quinazoline (4.76) was not possible due to the low acidity of the thiomethyl protons

The benzothiazole-2-ylsulphenyl group directed the lithiation of 2-(benzothiazole-2-ylthio)pyridine (4.97) to the 3-position of the pyridine ring. The presence of a sulfur substituent on that ring will allow further transformations to be investigated.

4.4 Experimental

General instrumental details were given in Section 2.4. The 300 MHz ^{1}H-n.m.r. spectrum was recorded by Dr. W. S. Brey on a Nicolet NT-300 spectrometer.

Dimethylformamide (DMF) was stored over 4Å molecular sieves. Dichloromethane was dried over $CaCl_2$, distilled and stored over 4Å molecular sieves. Tetrahydrofuran (THF) and diethyl ether were dried by refluxing over sodium with benzophenone as indicator. Butyllithium was purchased from Aldrich Chemical Co. as a solution in hexane and regularly titrated using a standard procedure [76JO1879]. Diisopropylamine was refluxed and distilled over calcium hydride, and then stored over sodium hydroxide under Ar. All the reactions involving alkyllithium reagents were carried out under Ar atmosphere.

The following compounds were prepared by reported methods: 3-cyano-4,6-diphenyl-2-pyridone (4.29) (25%), m.p. 320-322 °C (lit. [30JIC481] m.p. 318-320 °C); di(benzothiazol-2-ylthio) methane (4.80) (60%), m.p. 90-95 °C (lit. [57MI31] m.p. 95-96.5 °C); 2-methylthiobenzothiazole (4.42) (79%), b.p. 105-110 °C/0.6 mmHg (lit. [49J1503] b.p. 174-175/22 mmHg); 2-ethylthiobenzothiazole (4.46a) (82%), b.p. 130-131 °C/1.5 mmHg (lit. [49J1503] b.p. 178 °C/18 mmHg); 2,4-dimercaptoquinazoline (4.67) (84%), m.p. 300-309 °C (decomp.) (lit. [47JA2138] m.p. 308-309 °C [decomp.]); benzothiazol-2-yldisulfide (4.99), m.p. 171-175 °C (lit. [23JA2396] m.p. 176 °C).

4.4.1 2-Alkoxypyridine Derivatives

Preparation of 4,6-diphenyl-2-pyridone (4.30)

3-Cyano-4,6-diphenyl-2-pyridone (4.29) (0.5g) was stirred and refluxed in 48% hydrobromic acid (50 ml) until all the solid dissolved (24-48h). On cooling the yellow solution, 4,6-diphenyl-2-pyridone(4.30) precipitated as white prisms (0.33g; 72%), m.p. 196-200 °C (lit. [30JIC481] m.p. 207-208 °C); ν_{max} (cm^{-1})($CHBr_3$) 1640(s), 1615(m), 1600(m); δ (p.p.m.) ($CDCl_3$) 9.2-8.1(b), 8.0-7.3(10H, m), 6.85(2H,s).

Preparation of phenylthiomethyl chloride (4.31)

Paraformaldehyde (7.5g, 250 mmol) was stirred in benzene (50 ml) and concentrated hydrochloric acid (100 ml) added dropwise (over 5 min) with stirring. The stirred mixture was heated to 30 °C (inner temperature) and thiophenol (22g, 200 mmol) was added dropwise (over 25 min). After the addition was half-complete, the mixture was heated to 40 °C (inner temperature) while the addition proceeded. After the addition was complete, the mixture was stirred and heated at 60 °C (inner temperature) in a water bath for 2½h. On cooling, the two layers were separated, and the organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure (20 mmHg) and the residual oil distilled to give 22.6g of product (4.31) (71%), b.p. 90-95 °C/3.5 mmHg (lit. [74JO2648] b.p. 66 °C/0.2 mmHg). Phenylthiomethyl chloride has to be stored at -10 °C and protected against moisture to avoid decomposition.

Preparation of 2-benzyloxy-4,6-diphenylpyridine (4.33)

To a stirred solution of sodium ethoxide (2 mmol) in ethanol (1 ml), 4,6-diphenyl-2-pyridone (4.30) (0.5g, 2 mmol) was added. After the solid dissolved completely, the solvent was removed under reduced pressure (20 mmHg) and the remaining sodium 2-oxido-4,6-diphenylpyridine (4.32) dried at 60 °C/1 mmHg. This solid was dissolved in DMF (6 ml), benzyl chloride (0.3g, 2.43 mmol) added to the stirred solution and the mixture stirred at room temperature for 24h. The reaction mixture was then poured into ice and extracted with dichloromethane (3 x 10 ml). The organic extracts were washed with water (3 x 10 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure (20 mmHg) and the resulting solid stirred in methanol (20 ml) and filtered to give the product (4.33) as a white solid (0.5g, 73%), m.p. 121-123 °C (Found: C, 85.59; H, 5.56; N, 4.12%. $C_{24}H_{19}NO$ requires C, 85.45; H, 5.63, N, 4.15%); ν_{max} (cm^{-1}) ($CHBr_3$) 1610(m), 1600(m), 1580(m), 1550(s), 1500(m), 1450(m), 1430(m), 1400(s), 765(s) δ (p.p.m.) ($CDCl_3$) 8.5-8.2(2H, m), 8.0-7.3(14H, m), 7.2(1H, s), 5.7(2H, s).

Preparation of 2-(phenylthiomethoxy)-4,6-diphenylpyridine (4.14)

4,6-Diphenyl-2-pyridone (0.5g, 2 mmol) was added to sodium ethoxide (2 mmol) in ethanol (5 ml). After the solid dissolved completely, the solvent was removed in vacuo and the solid dried (60 °C/1 mmHg). This sodium salt was then dissolved in DMF (6 ml) and phenylthiomethyl chloride (4.31) (0.38g,

2.43 mmol) added with stirring. The mixture was stirred at 25 °C for 20h, cooled in ice and water (10 ml) added to it. The mixture was extracted with dichloromethane (2 x 10 ml), and the organic layer washed with water (3 x 10 ml) and dried over $MgSO_4$. Evaporation of the solvent gave an oil that upon stirring in methanol afforded the product (4.14) as a white solid (0.34g, 45%), m.p. 65-67 °C (Found: C, 77.64; H, 5.17; N, 3.59%. $C_{24}H_{19}NOS$ requires C, 78.04; H, 5.14; N, 3.79%); ν_{max} (cm^{-1}) ($CHBr_3$) 1610(s), 1600(s), 1580(m), 1550 (s), 1390(s), 1190(s), 760(s); δ (p.p.m.) ($CDCl_3$) 8.2 (2H, m), 8.0-7.3(14H, m), 7.1(1H, s), 6.1(2H, s).

Reaction of 2-(phenylthiomethoxy)-4,6-diphenylpyridine (4.14) with n-butyllithium

To a stirred solution of (4.14) (0.37g, 1 mmol) in THF (13 ml), at 25 °C 1.6M n-butyllithium in hexanes (0.62 ml, 1 mmol) was added dropwise. The resulting red solution was stirred at 25 °C for 30 min. Benzyl chloride (0.15g, 1.2 mmol) in THF (1 ml) was added to the solution and the mixture stirred overnight at room temperature. The solvent was removed in vacuo (20 mmHg) and the residue was extracted between water and dichloromethane. The organic extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated and the remaining oil stirred in petroleum ether to give 4,6-diphenyl-2-pyridone (4.30)(0.1g, 40%), identical to the compound previously prepared (vide supra) in spectral (i.r., ^{1}H-n.m.r.) properties.

Preparation of 4,6-diphenyl-2-(phenylsulfonylmethoxy)pyridine (4.37)

m-Chloroperbenzoic acid (10 mmol) was added with stirring to a solution of (4.14) (1.84g, 5 mmol) in dichloromethane (50 ml) at 0 °C. The mixture was stirred at 0 °C for 1½h and at 25 °C for further 5h. After filtration, the solution was washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated (20 mmHg), and the remaining oily solid dried (25 °C/0.1 mmHg). Stirring in petroleum ether with a few drops of methanol afforded 1.73g (90%) of the product (4.37), m.p. 124-125 °C (Found: C, 71.86; H, 4.72; N, 3.33%. $C_{24}H_{19}NO_3S$ requires C, 71.82; H, 4.73, N, 3.49%); ν_{max} 1608(s), 1598(s), 1580(m), 1550(s), 1498(m), 1480(w), 1445(m), 1430(m), 1400(m), 1390(m), 1355(m), 1320(s), 1310(m), 1300(m), 1260(m), 1230(w), 1190(s), 1110(m), 1075(s), 1050(m), 1025(m), 950(w), 890(m), 860(m); δ (p.p.n.) ($CDCl_3$) 8.1(4H, m), 7.9-7.4(12H, m), 7.0(1H, s), 5.8(2H, s). ^{13}C-N.m.r. data are given in Table 4.1.

Preparation of 4,6-diphenyl-2-[2-phenyl-1-(phenylsulfonyl)-ethoxy]pyridine (4.38a)

To a stirred solution of the sulfone (4.37) (0.2g, 0.5 mmol) in THF (5 ml) at -78 °C, 1.5M n-butyllithium (0.5 ml, 0.75 mmol) was added dropwise. The resulting brown solution was stirred at -78 °C for 1h and benzyl chloride (0.095g, 0.75 mmol) in THF (2 ml) was then added. After stirring at -78 °C for 1h, the solution was allowed to warm slowly to 25 °C. The solvent was removed in vacuo (20 mmHg) and the residue was extracted between diethyl ether and water; the organic extracts

were diluted with dichloromethane (20 ml), dried over $MgSO_4$ and the solvent removed under reduced pressure (20 mmHg). The residue was stirred in petroleum ether with a few drops of methanol. This afforded the product (4.38a) as a creme solid (0.15g, 61%), m.p. 162-164 °C (Found: C, 75.78; H, 5.08; N, 2.86%. $C_{31}H_{25}NO_3S$ requires C, 75.76; H, 5.09; N, 2.85%); ν_{max} (cm^{-1}) ($CHBr_3$) 1610(s), 1600(m), 1550(s), 1500(m), 1450(m), 1435(m), 1395(m), 1360(m), 1320(s), 1310(s), 1195(s), 1115(m), 1080(m), 1060(m), 1030(m), 860(m), 760(s); δ (p.p.m.) ($CDCl_3$) 8.3-7.0(22H, m), 6.9(1H, s), 4.0-3.1(2H, ABX, J_{AB}=14 Hz, J_{AX}= 3 Hz, J_{BX}=10 Hz). ^{13}C-N.m.r. data are given in Table 4.1.

Preparation of 2-[2-hydroxy-2-phenyl-1-(phenylsulfonyl)ethoxy]-4,6-diphenylpyridine (4.38b)

n-Butyllithium (1.4 M in hexane) (0.41 ml, 0.6 mmol) was added to a stirred solution of the sulfone (4.37)(0.2g, 0.5 mmol) in THF (3 ml) at -78 °C. The solution was stirred at -78 °C for 20 min. Benzaldehyde (0.063g, 0.6 mmol) in THF (1 ml) was added, the solution stirred at -78 °C for 1h and then allowed to warm slowly to 25 °C. The solvent was evaporated, the residue treated with water and extracted with dichloromethane; the organic extracts were dried over $MgSO_4$, the solvent evaporated and the residue stirred in diethyl ether to give the product (4.38b) as a white solid (0.12g, 47%). The analitically pure material was obtained by washing the crude crystals with cold methanol, m.p. 151-153 °C (Found: C, 73.12; H, 4.88; N, 2.68%. $C_{31}H_{25}NO_4S$ requires C, 73.37;

H, 4.93; N,2.76%); ν_{max} (cm^{-1}) ($CHBr_3$) 3600-3500(m, b), 1610(s), 1600(s), 1580(m), 1550(s), 1500(m), 1450(s), 1430(m), 1390(s), 1360(s), 1310(s), 1260(m), 1240(m), 1190(s), 1080(s), 1050(m), 1030(m), 1000(w), 945(w); δ (p.p.m.) ($CDCl_3$) 8.1-7.2(21H, m), 7.1-6.6(2H, m), 6.1-5.4(1H, m). ^{13}C-N.m.r. data are given in Table 4.1.

Reaction of the sulfone (4.37) with n-butyllithium and methyl iodide

n-Butyllithium (1.5M in hexane)(0.8 ml, 1.2 mmol) was added dropwise to a solution of the sulfone (4.37) (0.4g, 1 mmol) in THF (8 ml) at -78 °C. The resulting dark brown solution was stirred at -78 °C for 15 min. Then, methyl iodide (0.17g, 1.2 mmol) in THF (2 ml) was added, the mixture stirred at -78 °C for 1h and the temperature was then allowed to rise slowly to 25 °C. The solvent was evaporated and the residue extracted between water and dichloromethane; the organic extracts were dried over $MgSO_4$, the solvent evaporated and the residue stirred in petroleum ether with a few drops of methanol. This afforded 0.3g of the mixture of the monomethylated (4.38c) and the dimethylated (4.38d) sulfones in the ratio 12:1; ν_{max} (cm^{-1})($CHBr_3$) 1610(s), 1595(s), 1580(m), 1550(s), 1495(m), 1445(m), 1430(m), 1390(m), 1360(m), 1315(s), 1305(s), 1260(m), 1195(s), 1105(m), 1080(s), 1020(w), 1000(w), 990(w), 950(m), 860(m), 760(s), 745(m), 730(m); δ (p.p.m.) ($CDCl_3$) 8.2-6.7 [m, (4.38c) and (4.38d)], 2.1[s, $C(CH_3)_2$ (4.38d)], 1.8[d, J=7 Hz, $CHCH_3$ (4.38c)]. ^{13}C-N.m.r. data are given in Table 4.1.

Thermolysis of 4,6-diphenyl-2-[2-phenyl-1-(phenylsulfonyl) ethoxy]pyridine (4.38a)

The sulfone (4.38a) (0.24g; 0.5 mmol) was heated neat at 240°C for 1h. After cooling, the solid was triturated and stirred in diethyl ether, and filtered to give 0.05g (40%) of 4,6-diphenyl-2-pyridone (4.30) identical in spectral properties (i.r., ^{1}H-n.m.r.) to the authentic material (vide supra).

4.4.2 2-Alkylthiobenzothiazole Derivatives

Lithiation of 2-Methylthiobenzothiazole (4.42). Reactions with electrophiles

A solution of 2-methylthiobenzothiazole (4.42) (2.71g, 15 mmol) in THF (50 ml) was added dropwise to LDA [prepared from diisopropylamine (2.5 ml) and 2.35M n-butyllithium (7 ml, 16.5 mmol)] in THF (100 ml) at -78 °C. The temperature was kept below -70 °C all throughout the addition. The resulting yellow solution was stirred at -78 °C for 1h.

Reaction with methyl iodide

To the yellow solution of the lithiated species (4.45) described above, methyl iodide (2.34g, 16.5 mmol) was added and the solution stirred at -78 °C for 1h. The reaction mixture was poured into water (150 ml), the layers separated, the aqueous layer extracted with ether (3 x 50 ml), the combined organic extracts washed with water and dried over $MgSO_4$.

Evaporation of the solvent in vacuo (20 mmHg) left an oil that on distillation afforded 2-ethylthiobenzothiazole (4.46a) as a colorless oil (76%), b.p. 126-132 °C/1.5 mmHg (lit. [49J1503] b.p. 178 °C/18 mmHg); δ (p.p.m.) ($CDCl_3$) 8.1-7.6 (2H, m), 7.6-7.1(2H, m), 3.3(2H, q, J=8 Hz), 1.4(3H, t, J=8Hz).

Reaction with ethyl iodide

Ethyl iodide (2.57g, 16.5 mmol) was added to the yellow solution of the lithio-derivative (4.45) described above and the mixture stirred at -78 °C for 4h. The above work-up procedure gave 2-propylthiobenzothiazole (4.46b) (87%) in a mixture with 2-methylthiobenzothiazole (4.42) that was separated by g.c./mass spectroscopy; m/e (%) for (4.46b):209(22.5), 194(14.07), 181(11.72), 108(16.43), 69(13.41), 41(17.28); δ (p.p.m.) ($CDCl_3$) 8.1-7.6(2H, m), 7.6-7.1(2H, m), 3.3(2H, t, J=7 Hz), 1.8(2H, m), 1.0(3H, t, J=7 Hz).

Reaction with n-hexyliodide

The same procedure as described for ethyl iodide gave, with n-hexyl iodide (3.5g, 16.5 mmol), 2-heptylthiobenzothiazole (4.46c) (72%), as a light yellow oil, after flash chromatography on silica gel, eluted with dichloromethane: hexanes (1:1); b.p. 157 °C/0.8 mmHg (Found: C, 63.33; H, 7.23; N, 5.25%. $C_{14}H_{19}NS_2$ requires C, 63.39; H, 7.16; N, 5.28%); ν_{max} (cm^{-1}) (neat) 3060(w), 2980(s), 2965(s), 2880(s), 1560(w), 1460(s), 1450(s), 1430(s), 1380(w), 1310(m), 1275(m), 1240(m), 1125(w), 1075(m), 1020(m), 990(s), 930(w), 850(w), 750(s), 720(s), 705 (w), 670(w); δ (p.p.m.) ($CDCl_3$) 8.1-7.7(2H, m), 7.6-7.1(2H, m), 3.35(2H, t, J=7 Hz), 2.0-0.7(13H, m); ^{13}C-n.m.r. data are given in Table 4.2.

Reaction with benzophenone

The procedure described above gave with benzophenone (3g, 16.5 mmol) an oil that solidified on standing. The solid was crushed in hexanes and filtered to give 2-(benzothiazol-2-ylthio)-1,1-diphenylethane-1-ol (4.46d) (4.55g, 84%), white plates from methanol, m.p. 132-134 °C (Found: C, 69.18; H, 4.83; N, 3.65%. $C_{21}H_{17}NOS_2$ requires C, 69.42; H, 4.68; N, 3.85%); ν_{max} (cm^{-1}) ($CHBr_3$) 3500-3100(m, b), 3060(m), 1600(w), 1560(w), 1540(w), 1505(w), 1490(m), 1460(m), 1455(m), 1450(m), 1425(m), 1310(m), 1275(w), 1260(w), 1240(w), 1080(m), 1060(m), 1030(w), 1020(m), 1000(s), 770(m), 755(s), 735(m); δ (p.p.m.) ($CDCl_3$) 8.1-7.8(2H, m), 7.8-7.2(12H, m), 5.8(1H, s, OH), 4.3(2H, s); ^{13}C-n.m.r. data are given in Table 4.2.

Reaction with p-tolualdehyde

Procedure: as above. p-Tolualdehyde (1.98g, 16.5 mmol) gave a thick oil that was purified by flash chromatography on silica gel, eluted with dichloromethane. This afforded 2-(benzothiazol-2-ylthio)-1-(4-methylphenyl)ethane-1-ol (4.46e) (3.67g, 81%) as an oil that solidified on standing; the solid was crushed in hexanes and filtered, m.p. 81-84 °C (Found: C, 63.82; H, 5.02; N, 4.50%. $C_{16}H_{15}NOS_2$ requires C, 63.78; H, 4.98; N, 4.65%); ν_{max} (cm^{-1}) ($CHBr_3$) 3500-3100(m, b), 2920(m), 2860(m), 1610(w), 1555(w), 1505(m), 1450(m), 1420(s), 1310(m), 1270(w), 1240(m), 1080(m), 1050(m), 1020(s), 1000(s), 810(m), 750(s), 720(s); δ (p.p.m.) ($CDCl_3$) 8.1-7.7(2H, m), 7.7-7.1 (6H, m), 5.2(1H, dd, J_{AX}=7 Hz, J_{BX}=4 Hz), 5.0-4.3(1H, b, OH),

3.9-3.3(2H, m), 2.3(3H, s), ^{13}C-n.m.r. data are given in Table 4.2.

Reaction with trimethylsilyl chloride

Following the general procedure and using trimethylsilyl chloride (2.1 ml, 16.5 mmol) gave an oil that subjected to flash chromatography on silica gel, eluting with benzene: hexanes (1:2) yielded two products: First eluted was (benzothiazol-2-ylthio)bis(trimethylsilyl)methane (4.46g)(0.24g, 5%), as a colorless oil (Found: M^+, 325.0811. Calculated for $C_{14}H_{23}NS_2Si_2$: M^+, 325.0810); ν_{max} (cm^{-1}) (neat) 3060(m), 2960(s), 2900(m), 2860(m), 1550(w), 1450(s), 1420(s), 1310(m), 1240(s), 1125(m), 1070(m), 1000(s), 985(s), 860(s), 830(s), 760(s), 750(s), 720(s), 700(m), 680(m), 630(m), 610(m); δ (p.p.m.) ($CDCl_3$) 8.1-7.8(2H, m), 7.7-7.2(2H, m), 2.7(1H, s), 0.2(18H, s). The second compound to elute was (benzothiazol-2-ylthio)(trimethylsilyl)methane (4.46f) (3.26, 86%), b.p. 120 °C/1.3 mmHg (Found: C, 52.27; H, 6.02; N, 5.53%. $C_{11}H_{15}NS_2Si$ requires C, 52.17; H, 5.92; N, 5.53%); ν_{max} (cm^{-1}) ($CHBr_3$) 3060(w), 2960(m), 2880(w), 1460(m), 1450(m), 1425(m), 1380(w), 1310(w), 1250(m), 1070(w), 990(m), 840(s), 750(s), 720(m); δ (p.p.m.) ($CDCl_3$) 8.2-7.8(2H, m), 7.7-7.2(2H, m), 2.65(2H, s), 0.2(9H, s); ^{13}C-n.m.r. data are given in Table 4.2.

Reaction with methyl p-methylbenzoate

The general procedure described above was followed, using double amount of LDA (ca. 33 mmol) and methyl p-methylbenzoate

(2.7g, 18 mmol) as electrophile. The oil that resulted, solidified on standing; the solid was triturated in hexanes and filtered to afford (benzothiazol-2-ylthiomethyl)(4-methylphenyl)methanone (4.46h) (3g, 67%), white microcrystals from methanol, m.p. 94-95 °C (Found: C, 64.68; H, 4.35; N, 4.57%. $C_{16}H_{13}NOS_2$ requires C, 64.21; H, 4.34; N, 4.68%); ν_{max} (cm^{-1}) ($CHBr_3$) 2920(w), 1670(s), 1600(m), 1580(w), 1500(w), 1450(m), 1425(s), 1310(m), 1290(m), 1280(m), 1240(w), 1190(m), 1180(s), 1070(w), 990(s), 800(m), 750(s), 720(m); δ (p.p.m.) ($CDCl_3$) 8.2-7.7(4H, m), 7.7-7.2(4H, m), 5.0(2H, s), 2.4(3H, s); ^{13}C-n.m.r. data are given in Table 4.2.

Preparation of 1-heptanethiol from 2-heptylthiobenzothiazole (4.46c)

n-Butyllithium (4.4 mmol) was added to a solution of 2-heptylthiobenzothiazole (0.53g, 2 mmol) in THF (20 ml) at -78 °C. The resulting light yellow solution was stirred at -78 °C for 1½h. The reaction mixture was poured into water (20 ml) and extracted with diethyl ether (3 x 20 ml); the organic extracts were washed with brine, dried over $MgSO_4$ and the solvents evaporated in vacuo (20 mmHg) to give an oil. Flash chromatography on silica gel eluting with benzene afforded two products: 1-heptanethiol was eluted first (0.18g, 69%), b.p. 170-175 °C (lit. [82MI2866], b.p. 173-6 °C; δ (p.p.m.) ($CDCl_3$) 2.55(2H, pseudo q), 1.8-0.7(14H, m); δ_C (p.p.m.) ($CDCl_3$) 34.01(t), 31.67(t), 28.65(t), 28.26(t), 24.51(t), 22.51(t), 13.93(q). The second compound was 2-butylbenzothiazole (4.48) (0.3g, 79%); ν_{max} (neat) 3060(w), 2960(s),

2940(s), 2880(s), 1510(m), 1450(m), 1430(m), 1380(m), 1350(w), 1310(w), 1240(w), 1110(s), 1080(m), 1010(w), 900(s), 750(s), 730(s), 640(m); m/e (%) 191(0.67), 162(6.98), 149(34.71), 86 (27.33), 84(43.94), 74(17.69), 59(33.28), 45(34.88), 31(100); δ (p.p.m.) ($CDCl_3$) 8.3-7.8(2H, m), 7.8-7.2(2H, m), 3.1(2H, t), 2.1-0.7(7H, m); δ_C (p.p.m.) ($CDCl_3$) 171.64(s), 152.93(s), 134.75(s), 125.34(d), 124.12(d), 122.08(d), 121.01(d), 33.57(t), 31.28(t), 21.88(t), 13.35(q).

Lithiation of 2-ethylthiobenzothiazole (4.46a) with LDA/THF
Reaction with p-tolualdehyde

A solution of 2-ethylthiobenzothiazole (1.95g, 10 mmol) in THF (30 ml) was added dropwise to LDA [from diisopropylamine (3.4 ml) and 2.35M n-butyllithium (4.7 ml, 11 mmol)] in THF (60 ml). The resulting light yellow solution was stirred at -78 °C for 3h. p-Tolualdehyde (1.44g, 12 mmol) in THF (5 ml) was added dropwise, the solution stirred at -78 °C for 3h, poured into water (90 ml) and extracted with ether (3 x 30 ml). The organic extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave an oil that solidified on standing. The solid was triturated in cyclohexane and filtered to afford (benzothiazol-2-yl)(4-methylphenyl)methanol (4.52) (1.63g, 64%), recrystallized from diisopropyl ether, m.p. 127-130 °C (Found: C, 70.52; H, 5.26; N, 5.32%. $C_{15}H_{13}NOS$ requires C, 70.58; H, 5.09; N, 5.49%); ν_{max} (cm^{-1}) ($CHBr_3$) 3500-2500(s, b), 1610(w), 1600(m), 1550(w), 1500(s), 1430(s), 1370(m), 1310(s), 1280(m), 1240(m), 1060(s), 1040(s), 1100(s), 940(m), 870(m), 840(m), 820(s), 750(s), 720(s); δ (p.p.m.)

($CDCl_3$) 8.1-7.7(2H, m), 7.6-7.0(6H, m), 6.1(1H, s), 5.2-4.6 (1H, b, OH), 2.3(3H, s); δ_C (p.p.m.) ($CDCl_3$) 175.64(s), 152.59 (s), 138.40(s), 138.11(s), 135.14(s), 129.44(d), 126.66(d), 126.03(d), 125.0(d), 122.95(d), 121.69(d), 74.12(d), 21.15(q).

Lithiation of 2-ethylthiobenzothiazole (4.46a) with n-butyllithium/TMEDA/ether. Reaction with p-tolualdehyde

A solution of n-butyllithium (6 mmol) and TMEDA (0.9 ml, 6 mmol) in diethyl ether (10 ml) was added to 2-ethylthiobenzothiazole (0.97g, 5 mmol) in diethyl ether (50 ml) at -78 °C. The resulting yellow solution was stirred at -78 °C for 10 min, p-tolualdehyde (0.7 ml, 6 mmol) in ether (2 ml) was added, and the mixture stirred at -78 °C for 1½h. The reaction mixture was poured into water (50 ml), the aqueous layer extracted with ether (3 x 20 ml), the combined organic extracts washed with water and dried over $MgSO_4$. Evaporation of the solvent in vacuo (20 mmHg) left an oil that solidified on standing. The solid was stirred in cyclohexane and filtered to give 2-(benzothiazol-2-yl)-1-(4-methylphenyl)-2-propylethane-1-ol (4.58) (0.25g, 32%), m.p. 130-133 °C (Found: C, 72.97; H, 7.05; N, 4.29%. $C_{19}H_{21}NOS$ requires C, 73.31; H, 6.75; N, 4.50%); ν_{max} (cm^{-1}) ($CHBr_3$) 3580(w), 3500-3100(m, b), 2960(s), 2920(s), 2880(m), 1510(s), 1450(m), 1430(m), 1380(w), 1310(m), 1280(m), 1250(m), 1180(m), 1080(m), 1050(s), 1010(m), 830(m), 760(s), 730(s); δ (p.p.m.) ($CDCl_3$) 8.0-7.6(2H, m), 7.6-7.0 (6H, m), 4.95(1H, d, J=6 Hz), 4.2-3.6(1H, b, OH), 3.4(1H, pseudo q), 2.3(3H, s), 2.0-0.7(7H, m); δ_C (p.p.m.) ($CDCl_3$)

173.59(s), 152.73(s), 139.62(s), 137.09(s), 134.26(s), 128.95 (d), 126.12(d), 125.78(d), 124.66(d), 122.61(d), 121.35(d), 76.61(d), 51.80(d), 35.18(t), 21.0(q), 20.37(t), 13.79(q).

4.4.3 2-Mercaptoquinazoline Derivatives

Preparation of 4-(N,N-dimethylethylenediamino)quinazoline-2-thione (4.69)

N,N-Dimethylethylenediamine (95%) (0.15g, 1.6 mmol) was added to a suspension of 2,4-dimercaptoquinazoline (4.67) (0.31g, 1.6 mmol) in n-butanol (3 ml). The mixture was stirred and refluxed under a nitrogen atmosphere for 6h. After cooling, stirring was continued overnight at room temperature. The solvent was evaporated *in vacuo* (20 mmHg), the remaining solid mass triturated in hexanes and the resulting solid filtered to afford the product (4.69) (0.37g, 93%), microcrystals from acetonitrile, m.p. 176-178 ^{o}C (Found: C, 57.86; H, 6.62; N, 22.62%. $C_{12}H_{16}N_4S$ requires C, 58.06; H, 6.45; N, 22.58%; ν_{max} (cm^{-1}) ($CHBr_3$) 1620(s), 1600(s), 1560(s), 1540(s), 1530(s), 1460(m), 1420(m), 1380(m), 1350(m), 1330(s), 1280(m), 1200(s), 1060(w), 1030(w), 960(w), 745(m); δ (p.p.m.) ($CDCl_3$) 7.9-7.1(5H, m), 3.9(2H, t, J=6 Hz), 2.7(2H, t, J=6 Hz), 2.4(6H, s); δ_C (p.p.m.) (DMSO-d_6) 180.31(s), 156.15(s), 140.59 (s), 133.86(d), 123.39(d), 123.15(d), 115.43(d), 109.70(s), 57.51(t), 45.17(q), 38.73(t).

Preparation of N,N,N-trimethyl-2-[N'-(2-methylthioquinazoline-4-yl)amino]ethylammonium iodide (4.70)

The quinazoline-2-thione compound (4.69) (0.17g, 0.68 mmol) was dissolved in 1N NaOH (0.68 ml) with slight heating. to the solution at room temperature, methyl iodide (0.046 ml, 0.75 mmol) was added and the mixture stirred at room temperature for 15 min. The product (4.70) separated as white crystals that were filtered (0.09g, 60%), m.p. 228-230 °C (Found: C, 41.20; H, 5.18; N, 13.66%. $C_{14}H_{21}IN_4S$ requires C, 41.58; H, 5.19; N, 13.86%; ν_{max} (cm^{-1}) ($CHBr_3$) 3280(s), 2980(w), 2960(w), 2910(w), 1610(m), 1570(s), 1520(s), 1480(m), 1420(m), 1400(m), 1390(m), 1360(w), 1330(s), 1300(m), 1280(s), 1250(m), 1210(m), 1040(w), 1030(w), 950(m), 930(m), 910(m), 860(w), 810(w), 760(s); δ (p.p.m.) (DMSO-d_6) 8.7-8.3(1H, b, NH), 8.2-7.1(4H, m), 3.9-3.3(4H, m, b), 3.1(9H, s), 2.4(3H, s); δ_C (p.p.m.) ($CDCl_3$-DMSO-d_6) 165.04(s), 156.56(s), 147.96(s), 131.11(d), 124.38(d), 122.51(d), 120.93(d), 111.04(s), 61.84 (t), 51.20(q), 33.24(t), 11.83(q).

Preparation of 4-(N,N-dimethylethylenediamino)-2-(methylthio)-quinazoline (4.66)

The quinazoline-2-thione derivative (4.69) (4.96g, 20 mmol) was dissolved in ethanol(50 ml) and 1N HCl (30 ml). To this solution, methyl iodide (1.37 ml, 22 mmol) was added and the mixture stirred at room temperature for 35 min. The solution was extracted with dichloromethane (1 x 30 ml), the aqueous layer was made alkaline with 1N NaOH and extracted

with dichloromethane (3 x 30 ml). The organic extracts from the second extraction were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave the product (4.66) (4.5g, 86%) as a white solid, m.p. 104-107 °C (Found: C, 59.59; H, 7.24; N, 21.23%. $C_{13}H_{18}N_4S$ requires C, 59.54; H, 6.87; N, 21.37%); ν_{max} (cm^{-1}) ($CHBr_3$) 3400(w, b), 2960(w), 2940(w), 2920(w), 2820(w), 2780(w), 1610(m), 1580(s), 1550(m), 1520(m), 1440(w), 1400(w), 1360(m), 1350(m), 1330(m), 1280(m), 1250(w), 1210(w), 960(w), 950(w), 760(m); δ (p.p.m.) ($CDCl_3$) 7.9-7.2 (4H, m); 6.9-6.3(1H, b, NH), 3.7(2H, pseudo q), 2.65(5H, s and t), 2.3(6H, s); δ_C (p.p.m.) 167.32(s), 158.14(s), 149.60(s), 132.05(d), 125.96(d), 123.68(d), 121.05(d), 112.39(s), 56.93 (t), 44.64(q), 37.80(t), 13.58(q).

Attempted preparation of (4.77) in n-butanol

A mixture of 2,4-dimercaptoquinazoline (4.67) (0.31g, 1.6 mmol) and N,N,N'-trimethylethylenediamine (0.17g, 1.6 mmol) in n-butanol (3 ml) was stirred and refluxed under nitrogen for 8½h and stirred overnight at room temperature. The solid that precipitated, 4-butoxyquinazoline-2-thione (4.78)(0.13g, 35%), was filtered and recrystallized from n-butanol, m.p. 185-190 °C; ν_{max} ($CHBr_3$) 3110(m), 2960(s), 2910(m), 2890(m), 1620(s), 1600(m), 1550(s), 1490(m), 1470(m), 1420(s), 1360(m), 1340(m), 1310(m), 1270(m), 1250(w), 1200(s), 1160(m), 1110(s), 1100(s), 960(m), 900(w), 860(w), 830(w), 770(m), 750(m); δ (p.p.m.) ($CDCl_3$) 10.5-10.0(b, NH), 8.15(1H, d, J=8 Hz), 7.9-7.2(3H, m), 4.8(2H, t, J=7 Hz), 2.1-0.7(7H, m).

Preparation of 4-(N,N,N'-trimethylethylenediamino)quinazoline-2-thione (4.77)

A mixture of 2,4-dimercaptoquinazoline (4.67) (3.1g, 16 mmol) and 95% N,N,N'-trimethylethylenediamine (5.1g, 48 mmol) in toluene (40 ml) was stirred and refluxed under a nitrogen atmosphere for 60h. On cooling and refrigeration a solid precipitated. This was filtered to afford the product (4.77) (2.6g, 62%), m.p. 148-150 ^{o}C (Found: C, 59.69; H, 7.12; N, 20.84%. $C_{13}H_{18}N_4S$ requires C, 59.54; H, 6.87; N, 21.37%); ν_{max} (cm^{-1}) ($CHBr_3$) 3110(w), 2940(m), 2820(m), 2780(m), 1610(m), 1590(m), 1540(s), 1530(s), 1490(m), 1460(m), 1410(m), 1390(m), 1360(m), 1340(s), 1270(m), 1230(m), 1180(s), 1080(m), 1040(w), 1020(w), 920(w), 750(m); δ (p.p.m.) ($CDCl_3$) 8.15(1H, d, J=8 Hz), 7.9-7.2(3H, m), 4.1(2H, t, J=6 Hz), 3.6(3H, s), 2.8(2H, t, J=6 Hz), 2.35(6H, s); δ_C (p.p.m.) ($CDCl_3$) 177.74(s), 159.72(s), 142.87(s), 133.51(d), 126.37(d), 122.80(d), 116.19(d), 110.34 (s), 56.99(t), 51.14(t), 45.81(q), 40.96(q).

Preparation of 4-(N,N,N'-trimethylethylenediamino)-2-(methylthio)quinazoline (4.76)

The quinazoline-2-thione derivative (4.77) (2g, 7.63 mmol) was dissolved in a mixture of ethanol (100 ml), 1N HCl (12 ml) and water (20 ml). To this solution, methyl iodide (0.58 ml, 9.1 mmol) was added and the mixture stirred at room temperature for 1h. The solution was extracted with dichloromethane (1 x 50 ml), the aqueous layer was made alkaline with 1N NaOH and extracted with dichloromethane (3 x 50 ml). The organic extracts from the second extraction were washed with water

and dried over $MgSO_4$. Evaporation of the solvent afforded the product (4.76) as an oil (1.7g, 80%) that was analytically pure (Found: C, 60.68; H, 7.29; N, 20.23%. $C_{14}H_{20}N_4S$ requires C, 60.86; H, 7.24; N, 20.28%; ν_{max} (cm^{-1}) ($CHBr_3$) 2980(m), 2940(m), 2920(m), 2860(m), 2820(m), 2780(m), 1610(m), 1560(s), 1530(s), 1510(s), 1480(m), 1460(m), 1440(m), 1410(m), 1360(m), 1280(m), 1260(m), 1230(w), 1190(m), 1070(m), 1050(m), 960(m), 940(w), 890(w), 860(w), 760(m); δ (p.p.m.) ($CDCl_3$) 8.2(1H, d, J=8 Hz), 8.0-7.3(3H, m), 3.95(2H, t, J=7 Hz), 3.5 (3H, s), 2.65(5H, t and s), 2.4(6H, s); δ_C (p.p.m.) ($CDCl_3$) 166.15(s), 161.77(s), 152.64(s), 131.93(d), 126.66(d), 125.26 (d), 122.74(d), 113.44(s), 56.29(t), 51.02(t), 45.64(q), 40.20 (q), 13.82(q).

4.4.4 Benzothiazole-Dithioacetal Derivatives

Preparation of 2-[(phenylsulphenyl)methylthio]benzothiazole (4.81)

2-Mercaptobenzothiazole (4.44) (11.0g, 66 mmol) was dissolved in ethanol (20 ml) containing sodium ethoxide (66 mmol, from 1.63g of 97% NaH). Phenylthiomethyl chloride (4.31) (10.4g, 66 mmol) was added to the solution and the mixture stirred at room temperature for 1 3/4h. The solvent was removed in vacuo (20 mmHg) and the residue extracted between dichloromethane (50 ml) and water (20 ml), the organic extracts were dried over $MgSO_4$ and the solvent evaporated to give the product (17.2g, 90%) as an oil that could not be distilled without decomposition (Found: M^+, 289.0052. Calculated for $C_{14}H_{11}NS_3$: M^+, 289.0054); ν_{max} (cm^{-1}) ($CHBr_3$) 3030(m),

1580(w), 1475(m), 1450(m), 1420(s), 1360(w), 1305(m), 1270 (w), 1235(m), 1200(m), 1070(m), 1005(m), 990(s), 815(w), 750(s), 735(s), 720(s); ^{1}H- and ^{13}C-n.m.r. data are given in Tables 4.3 and 4.4, respectively.

Attempted metallation of (4.80) with $KOBu^{t}$/DMSO. Reaction with methyl iodide

Potassium t-butoxide (0.185g, 1.65 mmol) was added to a stirred solution of the dithioacetal (4.80)(0.52g, 1.5 mmol) in DMSO (10 ml). The solution was stirred at room temperature for 45 min, methyl iodide (0.23g, 1.65 mmol) added and the mixture stirred at room temperature for 9h. Further 0.185g of potassium t-butoxide were then added, the mixture stirred for 10 min, methyl iodide (0.1 ml) added and stirring continued overnight at room temperature. The reaction mixture was then poured into water (10 ml) and extracted with chloroform (3 x 10 ml); the organic extracts were washed with water (3 x 10 ml) and dried over $MgSO_4$. Evaporation of the solvent gave an oil that was identical in ^{1}H- and ^{13}C-n.m.r. properties to 2-methylthiobenzothiazole (4.42), prepared by a literature method (vide supra); δ (p.p.m.) ($CDCl_3$) 8.1-7.6(2H, m), 7.6-7.1(2H, m), 2.7(3H, s). ^{13}C-N.m.r. data are given in Table 4.2 (Section 4.2.2).

Lithiation of dithioacetals (4.80) and (4.81). Reaction with electrophiles

Typical procedure: n-Butyllithium (2.2 mmol) was added dropwise to a solution (4.80) or (4.81) (2 mmol) in THF (20 ml) at -78 ^{o}C and the resulting solution was stirred for 1h at this temperature.

Reactions with benzyl bromide

To the solution described above benzyl bromide (2.2 mmol) dissolved in THF (2 ml) was added. The reaction mixture was stirred at -78 °C for 1h and then at -40 °C for 4h. It was quenched with water (15 ml), extracted with dichloromethane (3 x 15 ml), the organic extracts dried over $MgSO_4$ and the solvent evaporated in vacuo (20 mmHg).

1,1-Di(benzothiazol-2-ylthio)-2-phenylethane (4.87b) was obtained from (4.80) as an oil that crystallized on stirring in petroleum ether. Yield: 66%; needles from ethanol, m.p. 131-132 °C (Found: C, 60.60; H, 3.63; N, 6.28%. $C_{22}H_{16}N_2S_4$ requires C, 60.55; H, 3.66; N, 6.42%); ν_{max} (cm^{-1}) ($CHBr_3$) 3040(w), 1510(w), 1490(w), 1450(m), 1420(s), 1310(m), 1270(w), 1240(m), 1070(m), 1015(m), 990(s), 930(w), 750(s), 720(m); ^1H- and ^{13}C-n.m.r. data are given in Tables 4.3 and 4.4, respectively.

1-(Benzothiazol-2-ylthio)-2-phenyl-1-(phenylthio)ethane (4.88b) was obtained from (4.81) in 83% yield after stirring in 95% ethanol the residue from evaporation, microcrystals from absolute ethanol, m.p. 87-90 °C (Found: C, 66.23; H, 4.55; N, 3.60%. $C_{21}H_{17}NS_3$ requires C, 66.49; H, 4.48; N, 3.69%); ν_{max} (cm^{-1}) ($CHBr_3$) 3030(m), 2860(w), 1600(w), 1580(m), 1490(m), 1480(m), 1460(m), 1450(m), 1440(m), 1420(m), 1310(m), 1270(w), 1235(m), 1070(m), 1020(m), 1015(m), 990(s), 930(m), 825(w), 750(s), 720(m); ^1H- and ^{13}C-n.m.r. data are given in Tables 4.3 and 4.4, respectively.

Reaction with methyl idodide

To the solution described above, prepared from (4.81), methyl iodide (2.2 mmol) in THF (2 ml) was added and the solution stirred at -78 °C for 5h. The reaction mixture was worked-up as above. 1-(Benzothiazol-2-ylthio)-1-(phenylthio)-ethane (4.88a) was obtained in 80% yield as an oil (Found: M^+, 303.0227. Calculated for $C_{15}H_{13}NS_3$: M^+, 303.0210); ^1H- and ^{13}C-n.m.r. data are given in Tables 4.3 and 4.4, respectively.

Reaction with p-tolualdehyde

To the solution described above, prepared from (4.80), p-tolualdehyde (2.2 mmol) in THF (2 ml) was added and the mixture stirred at -78 °C for 1 3/4h. The reaction mixture was quenched with methanol, extracted between water and chloroform, the organic extracts washed with water, dried over $MgSO_4$ and the solvent evaporated under reduced pressure (20 mmHg). 2,2-Di(benzothiazol-2-ylthio)-1-(4-methylphenyl)ethane-1-ol (4.87c) was obtained in 83% yield as a thick oil; ^1H- and ^{13}C-n.m.r. data are given in Tables 4.3 and 4.4, respectively.

Reaction of (4.81) with LDA and benzoyl chloride

A solution of (4.81) (0.57g, 2 mmol) in THF (10 ml) was added dropwise to a solution of LDA (4.4 mmol) [from diisopropylamine (0.67 ml) and n-butyllithium (4.4 mmol)] in THF (5 ml) at -78 °C and the resulting dark green solution stirred at -78 °C for 1½h. Benzoyl chloride (0.25 ml, 2.2 mmol) in THF (2 ml) was then added and the mixture stirred at -78 °C for 30 min. The reaction mixture was then quenched with methanol and allowed

to warm to 25 °C, after which it was poured into water and extracted with chloroform. The organic extracts were washed with water and dried ($MgSO_4$). Evaporation of the solvent gave the benzoylated product (4.88d) (0.60g, 76%) as a gummy solid that could not be crystallized. ^1H- and ^{13}C-n.m.r. data are given in Tables 4.3 and 4.4, respectively.

4.4.5 Lithiation of 2-(Benzothiazol-2-ylthio)pyridine. Preparation of 2-(benzolthiazol-2-ylthio)pyridine (4.97)

2-Mercaptobenzothiazole (4.44)(31.5g, 188 mmol) was added to a solution of KOH (12.4g) in ethanol (100 ml) and the mixture stirred until complete dissolution took place. The solvent was evaporated under reduced pressure (20 mmHg) and the remaining solid was dried in vacuo (60 °C/1 mmHg). The solid was dissolved in DMF (70 ml) and 2-bromopyridine (20g, 126 mmol) added to the solution. The mixture was stirred and refluxed for 14h and stirred overnight at room temperature. The solvent was removed under reduced pressure (10 mmHg) and the residue extracted between benzene and water. The organic layer was washed with 1N NaOH, followed by water and dried over $MgSO_4$. Evaporation of the solvent gave an oil that solidified on standing. The solid was triturated in cyclohexane to afford the product (4.97) as a white-creme solid (14.4g, 42%), m.p. 63-65 °C (Found: C, 59.20; H, 3.24; N, 11.46%. $C_{12}H_8N_2S_2$ requires C, 59.01; H, 3.27; N, 11.47%; ν_{max} (cm^{-1}) ($CHBr_3$) 1570(m), 1510(w), 1450(m), 1410(s), 1310(w), 1280(w), 1240(w), 1090(w), 1040(w), 1020(w), 1000(m), 990(m), 760(s), 720(m); δ (p.p.m.)

8.7(1H, d), 8.2-7.1(7H, m); δ_C (p.p.m.) ($CDCl_3$) 162.14(s), 154.20(s), 152.29(s), 149.52(d), 137.04(d), 135.82(s), 125.83 (d), 124.66(d), 122.0(d), 120.66(d).

Lithiation of 2-(benzothiazol-2-ylthio)pyridine (4.97) with LDA/THF. Reaction with p-tolualdehyde

A solution of (4.97) (1.22g, 5 mmol) in THF (10 ml) was added to LDA [made from diisopropylamine (0.92 ml) and 1.9M n-butyllithium (3.16 ml, 6 mmol)] in THF (40 ml). The resulting strong red solution was stirred at -78 °C for 1h. p-Tolualdehyde (0.7 ml, 6 mmol) was added and the solution stirred at -78 °C for 1h. The reaction mixture was poured into water (50 ml) and extracted with chloroform (3 x 40 ml). The organic extracts were washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a gummy solid that crystallized upon stirring in hexanes to give 2-(benzothiazol-2-ylthio)-3-[hydroxyl(4-methylphenyl)methyl]pyridine (4.101) (1.0g, 55%), recrystallized from benzene, m.p. 150-153 °C (Found: C, 66.24; H, 4.42; N, 7.60%. $C_{20}H_{16}N_2OS_2$ requires C, 65.93; H, 4.39; N, 7.69%); ν_{max} (cm^{-1}) ($CHBr_3$) 3400-3100(m, b), 1570(m), 1560 (m), 1500(w), 1440(m), 1410(s), 1400(s), 1310(m), 1270(m), 1240(m), 1200(w), 1170(m), 1080(s), 1030(s), 1010(m), 850(m), 810(s), 790(m), 760(m), 750(s), 740(m), 720(m); δ (pp.m.) (DMSO-d_6) 8.8(1H, d), 8.5-8.0(3H, m), 7.9-7.2(7H, m), 6.4(1H, d, J=4 Hz, OH), 6.2(1H, d, J=4 Hz), 2.3(3H, s); δ_C (p.p.m.) (DMSO-d_6) 161.16(s), 149.76(s), 148.69(s), 145.81(d), 138.75 (s), 137.72(s), 134.85(s), 133.77(d), 133.53(s), 126.95(d), 125.29(d), 124.17(d), 122.81(d), 121.01(d), 119(84(d), 119.35 (d), 68.95(d), 18.95(q).

Lithiation of (4.97) with LDA/THF. Reaction with benzyl bromide

The reaction was carried out following an identical procedure to that described above for p-tolualdehyde. The reaction time was 5½h. After the same work-up procedure, the reaction mixture was subjected to flash chromatography (silica gel, dichloromethane) to afford 2-benzylbenzothiazole (4.104) (ca. 60 mg) as an oil (Found: M^+, 257.0317. Calculated for $C_{14}H_{11}NS$: M^+, 257.0332); δ (p.p.m.) ($CDCl_3$) 8.1(2H, m), 7.9-7.3(7H, m), 4.7(2H, s); δ_C (p.p.m.) ($CDCl_3$) 166.33(s), 153.12(s), 136.16(s), 135.29(s), 129.10(d), 128.66(d), 127.68(d), 126.03(d), 124.22 (d), 121.54(d), 120.96(d), 37.71(t).

Lithiation of (4.97) with LDA/THF. Reaction with trimethylsilyl chloride

A solution of LDA [2.2 mmol; from diisopropylamine (0.37 ml) and 2.3M n-butyllithium (0.95 ml, 2.2 mmol)] in THF (5 ml) was added to 2-(benzothiazol-2-ylthio)pyridine (4.97) (0.49g, 2 mmol) in THF (15 ml) at -78 °C; the temperature was maintained below -70 °C all throughout the addition. The resulting red solution was stirred at -78 °C for 1h. Trimethylsilyl chloride (0.28 ml, 2.2 mmol) was added and the solution stirred at -78 °C for 6h, after which a precipitate had formed. The reaction mixture was poured into water (20 ml) and extracted with dichloromethane (3 x 20 ml). The organic extracts were washed with water, dried over $MgSO_4$ and the solvents evaporated under reduced pressure (20 mmHg) to afford an oil. 2-(benzothiazol-2-ylthio)-3-(trimethylsilyl)pyridine (4.102) (0.17g, 27%) was obtained after flash chromatography on silica gel eluting with

dichloromethane, needles from hexanes, m.p. 97-98 °C (Found: C, 56.84; H, 5.15; N, 8.65%. $C_{15}H_{16}N_2S_2Si$ requires C, 56.96; H, 5.06; N, 8.86%); ν_{max} (cm^{-1}) ($CHBr_3$) 2960(m), 2800(w), 1550(m), 1510(w), 1450(m), 1420(m), 1410(m), 1360(s), 1310(m), 1260(w), 1250(s), 1200(m), 1180(m), 1160(m), 1130(m), 1010(m), 1000(s), 840(s), 790(m), 750(s), 720(m); δ (p.p.m.) ($CDCl_3$) 8.7(1H, m), 8.2-7.1(6H, m), 0.4(9H, s); δ_C (p.p.m.) ($CDCl_3$) 164.43(s), 158.34(s), 152.15(s), 149.57(d), 143.47(d), 137.14 (s), 135.58(s), 125.83(d), 124.37(d), 122.13(d), 121.93(d), 120.62(d), -0.87(q).

Lithiation of (4.97) with n-butyllithium/ether. Reaction with p-tolualdehyde

n-Butyllithium (2.2 mmol) was added dropwise to a solution of (4.97) (0.49g, 2 mmol) in diethyl ether (20 ml) at -78 °C and the solution was stirred at -78 °C for 1h. p-Tolualdehyde (0.26 ml, 2.2 mmol) in ether (2 ml) was added and the mixture stirred at -78 °C for 4h. Work-up with dichloromethane and water, as described above, gave an oily solid that was stirred in cyclohexane and filtered to afford (benzothiazol-2-yl)(4-methylphenyl)methanol (4.52) (0.32g, 62%), m.p. 124-126 °C, identical in spectral properties to the specimen previously prepared (see Section 4.2.2). Evaporation of the cyclohexane mother liquors gave an oil that was treated with dilute hydrochloric acid (3 ml) and extracted with ether (3 x 5 ml). The aqueous layer was made alkaline with 1M NaOH and extracted with ether (3 x 5 ml). The organic extracts

were dried over $MgSO_4$ and the solvent evaporated to give 2-butylthiopyridine (4.100)(Found: M^+, 167.0768. Calculated for $C_9H_{13}NS$: M^+,167.0768); δ (p.p.m.) ($CDCl_3$) 8.6(1H, d), 7.7-6.8(3H, m), 3.2(2H, t, J=7-8 Hz), 2.9-0.7(7H, m).

CHAPTER V
SUMMARY

Nitrogen heterocycles were used to promote carbanionic reactions through ylide formation, dipole stabilization and ortho-directing effects.

Thus, pyridinium ylides derived from 1-allyl- and 1-methyl-2,4,6-triphenylpyridinium salts reacted in carbanionic reactions with aromatic aldehydes to give the corresponding aldol products. The allyl adducts, upon heating in chlorobenzene underwent loss of 2,4,6-triphenylpyridine, followed by 1,2-aryl or H-shift to give crotonaldehydes and isomeric α, β-unsaturated ketones. The adducts derived from 1-methyl-2,4,6-triphenylpyridinium tetrafluoroborate gave quinolizinium salts on pyrolysis. The 1-methyl ylide was also added Michael-fashion to acrylonitrile to form the corresponding indolizine.

However, the ylide derived from 1-benzyl-2,4,6-triphenylpyridinium tetrafluoroborate underwent thermal rearrangement to form an azepine derivative. This is a novel method for the preparation of monocyclic azepines.

Nucleophilic displacement of the pyridine moiety in 2,4,6-trisubstituted pyridinium salts by hindered monosubstituted malonate anions was possible with 1-benzyl- and

1-secondary-alkyl-pyridinium salts. These gave disubstituted malonate esters in moderate yields. The analogous reaction between 1-primary-alkyl pyridinium salts and primary nitroamine anions gave mixtures of secondary nitroamines and the isomeric O-alkylacinitroamines. Pyridines can be displaced by many other nucleophiles from pyridinium salts [20T679, 84AG(E)420]. Therefore, the consecutive ylide-mediated transformation and nucleophilic displacement would achieve the α-functionalization of a primary amine and the conversion of the amino group into other functionalities.

However, the elimination of 4,6-diphenyl-2-pyridone from compounds derived from the corresponding 2-(phenylsulfonylmethoxy)pyridine by carbanionic reactions was not a useful transformation due to the high temperatures required.

The related carbanions derived from 2-methylthiobenzothiazole and 2-mercaptobenzothiazole dithioacetals reacted with a variety of electrophiles. When the electrophile used with 2-methylthiobenzothiazole was an alkyl halide, the removal of the heterocyclic moiety by n-butyllithium afforded an alkanethiol with one more methylene unit than the original halide. The analogous transformation starting from 2-ethylthiobenzothiazole could not be achieved due to the impossibility to lithiate 2-ethylthiobenzothiazole at the α-methylene position.

The benzothiazol-2-ylsulphenyl group was not only capable of stabilizing adjacent carbanions but it also did so with carbanions one carbon unit away. This was shown by the lithiation at the 3-position of the pyridine ring in 2-(benzothiazol-2-ylthio)pyridine. The corresponding 3-lithio derivative was probably stabilized by the inductive effect of the sulfur atom [83T2009] and the coordinative effect of the benzothiazole nitrogen.

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Throughout this work, references are designated by a number-letter coding of which the first two numbers denote tens and units of the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted. The system is based on that used in the monographs: (a) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides", Academic Press, New York, 1971; (b) J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "The Tautomerism of Heterocycles", in "Advances in Heterocyclic Chemistry", Supplement 1, Academic Press, New York, 1976.

The following additional notes apply:

1. A list of journals which have been assigned codes is given (in alphabetical order) together with their codes immediately following these notes. Journal names are abbreviated following the CASSI (Chemical Abstracts Service Source Index) system.

2. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) page number.

3. In the reference list the code is followed by the complete literature citation in the conventional manner.

4. For non-twentieth century references the year is given in full in the code.

5. For journals which are published in separate parts, the part letter or number is given (when necessary) in parantheses immediately after the journal code letters.

6. Less common journals and books are given the code "MI" for miscellaneous.

7. Where journals have changed names, the same code is used throughout, e.g. CB refers both to Chem. Ber. and to Ber. Dtsch. Chem. Ges.

Journals

Angew. Chem.	AG
Angew. Chem., Int. Ed. Engl.	AG(E)
Bull. Chem. Soc. Jpn.	BCJ
Bull. Soc. Chim. Fr.	BSF
Can. J. Res.	CJR
Chem. Abstr.	CA
Chem. Ber.	CB
Chem. Heterocycl. Compd. (Engl. Transl.)	CHE
Chem. Lett.	CL
Chem. Rev.	CR
Chem. Scr.	CS
Chimia	C
Heterocycles	H
J. Am. Chem. Soc.	JA
J. Chem. Soc.	J

J. Chem. Soc. Chem. Commun.	CC
J. Chem. Soc. Perkin Trans. I	J(PI)
J. Heterocycl. Chem.	JHC
J. Indian Chem. Soc.	JIC
J. Chem. Soc. Perkin Trans. II	J(PII)
J. Org. Chem.	JO
Khim. Geterotsikl. Soedin.	KGS
Liebigs Ann. Chem.	LA
Org. Magn. Reson.	OMR
Org. React.	OR
Pure Appl. Chem.	PAC
Q. Rev., Chem. Soc.	QR
Recl. Trav. Chim. Pays-Bas	RTC
Russ. Chem. Rev. (Engl. Transl.)	RCR
Synth. Commun.	SC
Synthesis	S
Tetrahedron	T
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BIOGRAPHICAL SKETCH

Jose Miguel Aurrecoechea Fernandez was born March 5, 1958 in Bilbao, Spain. He received the degree Licenciatura con Grado from Universidad del Pais Vasco, Bilbao, in July of 1980 under the direction of Professor Esther Dominguez. In January of 1981 he entered the University of Florida to begin graduate studies under the direction of Professor Alan R. Katritzky.

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Alan R. Katritzky,
Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Merle A. Battiste
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier, Jr.
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William M. Jones
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Zoran R. Pop-Stojanovic
Professor of Mathematics